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BULLETIN ON

NARCOTICS

Vol. XII, No. 2, APRIL - JUNE 1960

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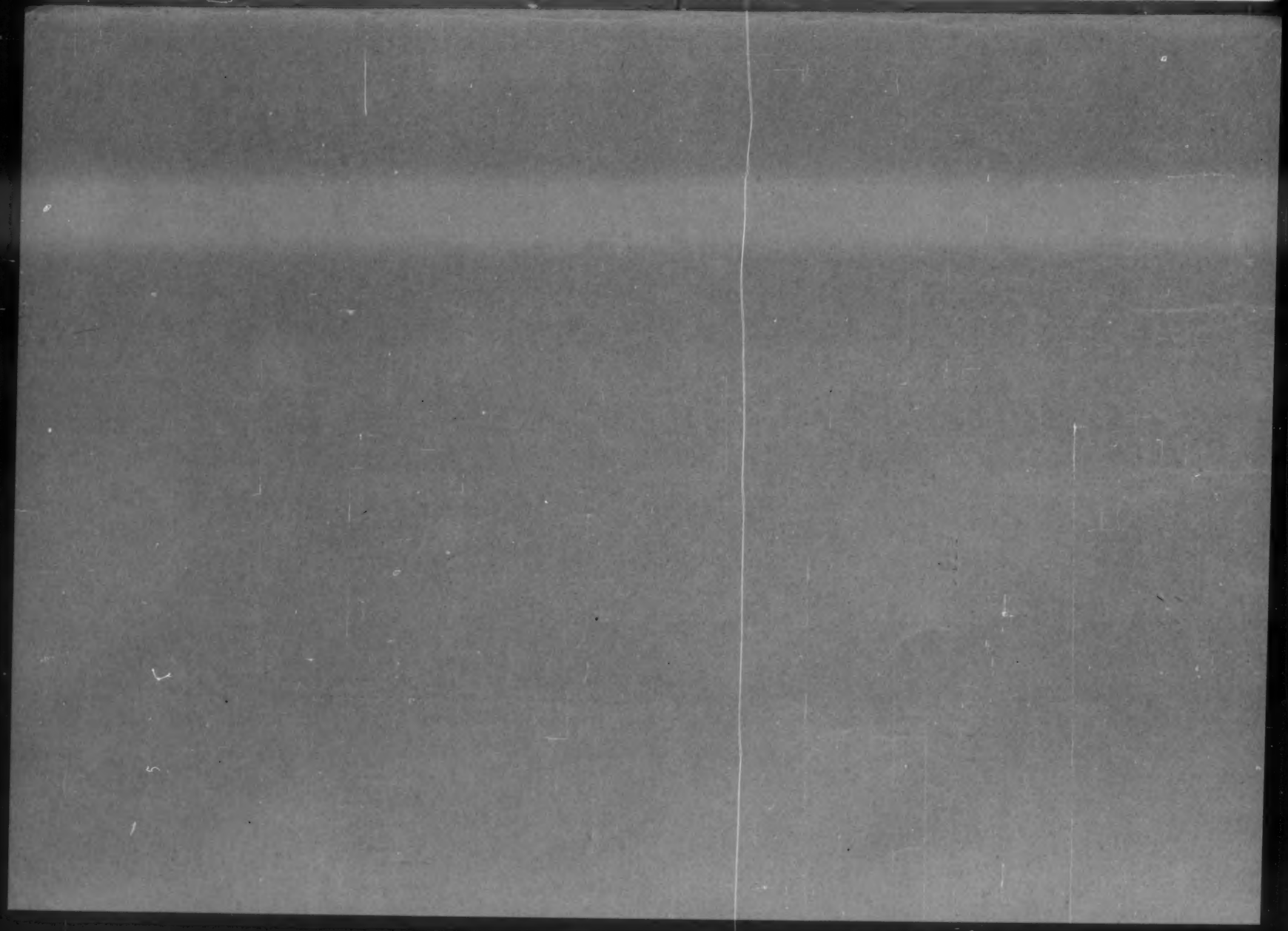

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Vol. XII, No. 2, APRIL-JUNE 1960

UNITED NATIONS

DIVISION OF NARCOTIC DRUGS

Geneva

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The new narcotics law in Iran

By Dr. A. H. Radji, Minister of Health of Iran

In my article, " Opium control in Iran — a new regime ",[1] I described briefly the administrative measures which had been taken in Iran, after three years' study of the operation of the 1955 Opium Law, to improve the control of the narcotics traffic into and in Iran. I alluded both to the present problems which face Iran in this field and to a new law which was at that moment before the Iranian Parliament for enactment.

The new Bill became law by an Act of Parliament dated 22 June 1959. It is now in force, under the auspices of the new administration, which I have already briefly described. This new law, in the confident opinion of the Government of Iran, represents a further important step forward in the struggle against the illicit traffic in narcotics in Iran. It is the purpose of the present article briefly to analyse and explain its more important provisions. In general, I shall confine myself, in the interests of clarity and brevity, to the articles of the law which introduce an improvement or a new provision.

In the first place, while the 1955 law dealt with opium only, experience has indicated that it is not advisable to dissociate opium from other narcotics in legislation. The high price and scarcity of opium which followed from the operation of the old law led addicts to look for other drugs; also the use of opium as a raw material for the manufacture of heroin was detected. The new law, therefore, covers both opium and other drugs. It also deals with the control of drugs used pharmaceutically, as well as with the prohibition of drugs which are habit-forming. The Ministry of Health is given the power to state what drugs will come under the purview of the Act as prohibited drugs, or as drugs liable to medical control at any time. In pursuance of this power, orders have already been issued placing over 60 drugs under the controls envisaged by the Act, in accordance with the principles laid down and the views expressed in the United Nations. Secondly, and following logically from what has been indicated already, the over-all responsibility for handling the drug traffic, legitimate as well as illicit, is laid upon the Ministry of Health, with the aid and co-operation of the other ministries which exercise administrative or executive functions that touch upon the operation of the Act, especially in relation to the illicit traffic. Thus, it is now enacted that the Ministry of Health shall control the import of drugs needed for legal purposes through a state monopoly, and that such imports shall be in the phrase sanctioned by the approval of the United Nations: for medical and scientific purposes only. In regard to the illicit traffic, regulations may be issued by the Ministry of Health governing the enforcement of the law, which is co-ordinated for practical purposes by the new general administration.[2]

The third, and perhaps the most important part of the new law, which takes up the greater part of the Act, is the re-definition of offences, the strengthening of penal provisions, and a clear statement of the legal position as to the confiscation of vehicles and material used in the illicit traffic. What I may call general offences are manufacture, preparation, import, sale or offering for sale of narcotics as defined in the Act. Penalties range from 5 to 15 years' imprisonment with fine for a first offence, to life imprisonment for repeated offences. Judges have discretion in relation to the sentences which they may impose under the maximum sentence allowed by the Act for an offence. But the death penalty is provided where the repeated offence is the illegal manufacture or the illegal import of narcotics.

The provisions which deal with the illegal cultivation of the opium poppy have been remodelled from those which were laid down in the 1955 law; they have been clarified and strengthened. An offence may involve imprisonment of up to 15 years with a fine amounting to 100,000 rials[3] per hectare of land used in illicit cultivation, and the destruction of the plantation. A distinction is drawn between cultivation under order of a landlord, for instance, and cultivation by the landlord. In the first case, the minimum punishment provided by the law will be inflicted on the cultivator, whereas in the second case the maximum penalty will be inflicted on the person under whose order the cultivation took place. Life imprisonment is provided for repeated offences. A government officer who fails to report cultivation or fails to take action on a report of illicit cultivation is liable to discharge from service and to 3 years' imprisonment. Keeping or concealing the seeds or capsules of the opium poppy involve imprisonment for from 2 months to 3 years.

Apart from what I have called general penal provisions, there are important special penal provisions, dealing with offences that were omitted from or not clearly defined in the old law. Thus, the using of premises for the consumption of narcotics is an offence punishable by a fine of up to 100,000 rials and 10 years' solitary confinement. It is also now an offence to profit from the running of such premises, while an employee in such a place is liable to 2 years' imprisonment. It is now an offence, again, to give facilities for the operation of such premises. On conviction of the owner, lessor or financier, the premises will be closed. Again, the possession, concealment or transportation of drugs are offences involving sentences of up to 3 years' imprisonment, or fine. If the quantity involved is over 50 g of opium or 1 g of any other narcotic, a court may impose up to 10 years' solitary confinement. Finally, it is an offence involving a punishment which may extend to 3 years' imprisonment to inject narcotics without medical prescription. If the drug be morphine

[1] See *Bulletin on Narcotics*, vol. XI, No. 1.
[2] *Ibid.*
[3] About U.S. $1,400.

or heroin, the maximum penalties provided in the Act can be imposed.

An important provision is the article under which priority of application is granted to this Act where its provisions clash with those of any other law. Adulterated drugs, a category which includes most drugs found in the illicit traffic in Iran, are treated as if they were pure for the purpose of the imposition of penalties. Informers, on whom most enforcement work depends, are closely connected with traffickers; in the eyes of the law, they are criminals; but it is possible to use them to combat the important criminal. Their liability to penalties for their own breaches of the law is therefore reduced. Seized vehicles become the property of the Ministry of Health, while seized drugs and material are placed at the disposal of the Narcotics Control Administration.

Operations under the Act are to be financed under a budget which will be subject to the approval of the Finance Ministry. But it is expected that there will be a continuing income to the Government from fines and from the disposal of seized material. This money is to be the basis of a special fund — after placing sufficient money on one side to pay rewards to the officers who have been instrumental in the discovery of offences — which will be used for the maintenance of a hospital, the cure of addicts, and the provision of material for the campaign against narcotics — an unusual example of poetic justice, in this case embodied in a legal enactment!

If it is found that a person adjudged to be guilty of an offence under the Act is, in fact, a drug addict, he is to be placed in hospital for treatment. The period spent in hospital will count as part of the sentence imposed on him. If he is cured of his addiction he may be released. There is an amnesty of one year covering persons who volunteer for hospital treatment in order to be cured of their addiction. The number of beds in the Teheran hospital has been increased from 50 to 100. The law, therefore, now contains both a statutory power to insist on the treatment of an addict who has been an accused before a court, and also an invitation to persons who have not been before a court but who wish to undergo a cure, to go to hospital without incurring the penalty provided by law for their offence of using a prohibited drug. It remains to be seen whether the facilities available and the funds which can be found to maintain them will suffice to meet the needs of the patients who may be expected to be treated at government hospitals under these provisions of the law. The rehabilitation of the addict is a cardinal point in the policy of the Government of Iran. It may not be possible to do all that is necessary in this field without aid from external sources.

Punishment is provided for officials of the Government appointed to exercise powers under this Act who fail to carry out their duties. They are liable to dismissal, and to the punishment provided for the offence with which they failed to deal. Employees of the Government or of public bodies who are found to be addicted to drugs are liable to dismissal or to be suspended from duty until they give up the habit. Lastly, the law protects the innocent citizen against the slanderous imputation that he is an addict or concerned with the sale of narcotics. If any such accusation is made in the press, and it cannot be proved on challenge, the person who is responsible for the publication of the slanderous report is liable to imprisonment for from 6 months to 1 year.

Strong penal provisions are useless unless there are courts which uphold the law vigorously and effectively. In view of the success of the special court for opium offences which has now operated in Teheran for some months, it was considered whether or not the system of special courts should be extended. It was felt, however, that the necessary effect could be produced by a provision in the law that priority must be given by the courts to narcotics cases in arranging their calendars of hearings. This provision is combined with a further stipulation that bail is not to be allowed in such cases; the accused are to be detained in custody till the hearing of the case.

The passing of so stringent a piece of legislation a little less than 4 years after the enactment of the law prohibiting the cultivation of the opium poppy and the use of opium represents an earnest of the determination of the Iranian Government to maintain a full, continuing pressure on traffickers and addiction in the struggle against narcotics. It embodies the results of a close study by the officers of the Government of Iran and its advisers of the working of the old laws, of the systems of control which exist in other countries, and of international legislation in this field. Thorough consideration of all aspects of the Bill and of the problems with which it is designed to cope took place in Parliament. This new law is an important development in the struggle against a social evil in which all good citizens both of a nation and of the international community are called on to play their part. It represents in itself one of the most complete, up-to-date acts of social legislation passed by any national government in this century. It does not neglect provision for an administration and for finance to carry out its provisions. It is therefore not merely idealistic; it is a practical down-to-earth legislative act. Iran awaits the outcome with confidence, fully realizing that the illicit traffic, fiercely attacked in one direction, will endeavour to break out in another. But the new law arms the Iranian administration with powers which will enable it to continue the struggle successfully, provided the full co-operation of her neighbours is assured. This co-operation is being actively sought and is promised; with it, even greater successes may be recorded than in the past.

The success of Iran's present effort in the country is exemplified by a series of raids on illicit laboratories, hide-outs and traffickers, which were reported in the Teheran press on 13 October 1959. As a result of these raids, 3 illicit laboratories for the manufacture of morphine and heroin were seized, and their owners arrested. In all, 81 traffickers were arrested, including the two most notorious opium smugglers in Iran, and 100 kg of opium and 6 kg of morphine and heroin were seized. One of the arrested smugglers had been carrying morphine and heroin on the Beyrouth - Baghdad - Teheran air route for some time. This is the heaviest blow struck at the illicit traffic in this region for years. It is the result of an investigation that had continued for several months, while the raids

were timed and carried out with a promptitude and efficiency that speak well for the officers and staff who were responsible for them.

In the international field, a protocol was negotiated with the Turkish Government during September 1959 which will result in far closer control over the illicit traffic in opium on the border between the two countries than had existed in the past. This is an apt reward for co-operation between two neighbouring countries which, it is hoped, will be followed generally. The need is emphasized by the discovery of smuggling of drugs by air into Iran alluded to in the previous paragraph. The recognition of the need is underlined both by these successful Turkish-Iranian negotiations, and also by the visit to Teheran in October 1959 of the United Nations Mission, which sought means of improving and extending such co-operation.

Cultivation of the opium poppy and opium production in Yugoslavia

By Vladimir Kušević
Director, Institute for the Control of Drugs, Zagreb (Yugoslavia)

Origin of the Cultivation

The opium poppy is not originally a Yugoslav plant. It was not until the nineteenth century that the Turks brought it into Macedonia, which was then under Turkish rule. Information on the origin of the crop is unreliable; it is only certain that cultivation on a large scale existed already about 1850. When it was found that the plant flourished, it soon became one of the most important crops in Macedonia (1).

The Plant

As in many other central European countries, the blue or black poppy, *Papaver somniferum var. nigrum*, a plant with violet flowers, dark blue to black seeds and open capsules, is grown in the northern part of Yugoslavia (Autonomous Region of Vojvodina and the People's Republic of Croatia). However, opium has never been obtained from this plant in Yugoslavia except at an experimental level, and its use for this purpose has not been sufficiently tested.

In the opium-producing districts of Yugoslavia, the " white poppy " is used almost exclusively for obtaining opium. The " white poppy " is a plant which has predominantly white flowers, nearly white or pale coloured seeds and closed capsules. It is mainly *Papaver somniferum var. album*, although not a pure strain of this plant, which is very seldom found, but a cross with the violet-grey species (2). The flowers are usually white or pale grey, with the lower part pale violet.

Individual plants with violet flowers may often be seen in fields of flowering poppy. Some cultivators eliminate such plants, because they consider that they yield weaker opium and less oil.

Such weeding out was tried for two years, first at the District Experimental Station at Kavadarci, and then over larger areas sown with seeds obtained from plants with violet flowers. Early results showed that they did not fall short of plants with white flowers and that the widely spread rumour of their poor quality was unfounded.

It should be borne in mind that this poppy with violet flowers differs from the aforementioned blue-black poppy cultivated in the northern areas of the country, and that, morphologically speaking, it is similar to the white opium poppy. In the Kočani area, there seems to exist another type of poppy with dark-coloured flowers which is characterized by a smaller number of stamens (3).

Attempts to transfer the Macedonian poppy to other districts of Yugoslavia and to other countries have not been successful. Plants grown from the best Macedonian seed have yielded opium of a weaker quality than they did in Macedonia.

Area of Cultivation

The opium poppy is grown in the central and eastern part of the People's Republic of Macedonia, mainly in the valley of the Vardar river, between the southern frontier with Greece and 42° 14′ northern latitude. The cultivation is found in five of the seven districts of the People's Republic of Macedonia — namely, Bitola, Kumanovo, Skopje, Štip and Titov Veles.

Cultivation is most intensive in the Štip and Titov Veles districts, which usually produce more than 80 per cent of the Yugoslav output.

Basic Conditions of Cultivation

Climate. — Climate is a highly important factor among the conditions of cultivation. The climatic conditions of the People's Republic of Macedonia are suitable for growing the opium poppy. These are a mild and damp winter, sometimes with a covering of snow, and a rapid transition to a very hot and dry summer.

Although this crop is destroyed by dry winters without snow, the plant can withstand temperatures as low as —5°C for short periods. A protective layer of snow is a very favourable factor, and in those conditions it can withstand a temperature of —10°C. Spring frosts are very dangerous because they can destroy the young plants.

At the beginning, the plants need a great deal of moisture in order to take root and develop properly, but at the end of their period of growth they need hot and dry weather; in such weather the alkaloid content increases.

The annual rainfall in the opium region of Yugoslavia is between 380 and 650 mm, while Ovče Polje (Štip) and Tikveš (Kavadarci) have an average of less than 450 mm. Nevertheless, these are the districts which produce opium of particularly high quality (4).

Wind presents a grave danger to the opium poppy before and during the incision of the capsule. Before the incision, a strong and warm wind is liable to dry the stems and capsules, so that they yield little latex. At the time of the incision of the capsules wind is dangerous because it causes them to knock against each other, so that the latex is lost or smeared over the capsules and therefore cannot be gathered.

Soil. — The plant does not need especially good soil and can grow on ground which is unsuitable for most other crops; however, it thrives better in manured, crumbly and light soil, exposed to the sun and protected from northern winds. Heavy

FIGURE 1

Map of the Federal People's Republic of Yugoslavia and the People's Republic of Macedonia

and clayey soil, as well as waterlogged soil, are not suitable. Waterlogged soil yields unduly thin latex, which gradually trickles down the capsule.

The soil is usually enriched with horse and cattle manure and the manure of small domestic animals; of late, fertilizers have been used (up to 300 kg of nitrogenous fertilizer and up to 700 kg of superphosphate per hectare). The fertilized soil often yields more than twice the amount of seeds, oil and opium than unfertilized ground. The composition of the soil is an essential factor on which the morphine content depends (5). The ground to be sown must be very carefully harrowed.

If all other conditions are fulfilled, the poppy flourishes best at altitudes not greatly above sea-level. Most of the cultivation is at less than 500 metres above sea-level and seldom as high as 800 metres.

Of the most important Yugoslav opium centres, Gevgelija is the lowest above sea-level (57 metres) and Kočani the highest (400 metres).

The Fruit

The fruit is a roundish or oval hollow capsule, 2.5 to 5 cm in diameter. On the upper part of the fruit, there is a radiate sear, remains of stigma, usually with 10 to 14 sides. The pedicle is short and is attached to the stem by a small bulging ring. The unripe pericarp is grey-green or blue-green in colour, while the ripe pericarp is yellowish.

The Seed

The seeds are obtained from selected, well-developed capsules. There are cultivators who leave some capsules uncut and take the seeds from them when they are quite ripe, because they believe that seeds from incised capsules are less likely to germinate (6). This practice is now becoming rather rare.

Seeds vary greatly in colour, from greyish white to light brown. In selecting seeds for sowing, no attention is paid to their colour or shade.

It has not been ascertained whether differences in the colour of seeds have any effect on the quantity or quality of opium.

The Processes of Plant Cultivation and Collecting Opium

The opium poppy is usually sown in the second half of September in two to four furrows, generally after the first autumn rains, which moisten the earth and promote proper germination.

In spite of the risk of a hard winter and spring frost to which autumn cultivation is exposed, spring sowing is rare and is in general resorted to only when autumn crops are destroyed during the winter. Spring sowing does not give such a large or good yield as autumn sowing. The long period of vegetation promotes the formation of alkaloids and, moreover, the spring crop may not develop sufficiently before the dry period and may wither without yielding either opium or seeds.

Spring sowing is carried out in the first fine days of the year, usually in the second half of February or the first half of March.

The seeds are very small, and are difficult to sow evenly. For this reason, in some places they are mixed with sand (2 to 4 kg of sand per kg of seed). Sowing with a seeder is carried out usually in rows at intervals of 30 to 40 cm. The earth is harrowed, so that the seeds are sown 1 or 2 cm deep. From 6 to 10 kg of seed are used to sow one hectare.

The spring operations are usually carried out in the second half of February and consist of pulling up grass and weeds, thinning (so that one plant should be approximately 10 cm away from the next) and banking up with earth. A second banking-up operation is usually carried out in the first half of March.

At the beginning of May, the fields become white with the flowering poppy, and when the flowers fall off, the capsules develop. Each plant yields from five to eight capsules.

The incisions are made before the capsules are quite ripe, ten to fifteen days after the flowers fall off, at the end of May or the beginning of June. The best time for making the incisions is determined by the colour and hardness of the capsules and by the appearance of a blue-brown ring at the bottom of the capsule. The period during which the capsules can be incised and the latex successfully collected does not

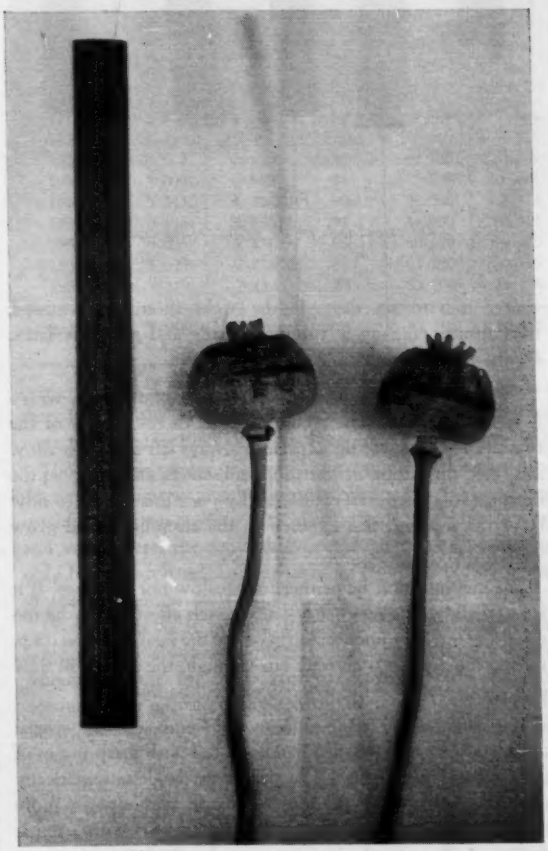

FIGURE 2

The incised capsules

FIGURE 3

Knives and tools for the incision of the capsules

exceed four to six days. If the right moment is missed, the capsules take on a yellowish shade and give less latex, finally yielding nothing at all.

Cutting is usually done between 11 a.m. and 5 p.m., with a horizontal incision which covers about three-quarters of the capsule. A quarter of the capsule is always left uncut, to allow a further circulation of nutritious substances at the top of the capsule. Small drops of white, milky juice then begin to flow from the incision, and exposed to the air solidify and grow darker.

The incision must be neither too shallow nor too deep. If it is too shallow, the number of latex vessels affected may be too small and too little juice will drip out; if the incision is too deep, so that the capsule is entirely cut through, the latex will flow into the capsule and the whole yield will be lost.

The incisions are made with special knives or with special tools, consisting of wooden handles fitted with sharp pieces of iron (often razor blades). The size of the blade automatically regulates the depth of the incision. Tools with two or more blades are also used, to allow two or three cuts with a single motion. As soon as the incision is made, the latex begins to drip. In order to avoid brushing against the capsules, the harvesters making incisions must walk backwards.

Unlike the procedure in certain Far Eastern countries the incisions are never repeated.*

At dawn the following day, the gathering of the raw opium begins; this consists of collecting the solidified drops of latex which have gathered overnight around the incision in the capsule. The opium is stripped from the capsule with a special blunt knife and is collected in a conical vessel attached to the harvester's belt or into a rumex or poppy leaf. It is then kneaded until it becomes dark, dried for a short time and thereupon is formed into 500- to 1,000-g cakes. That is the form in which it is delivered by the producers.

* It has been proved that two, three or more incisions yield more opium, but each subsequent incision produces opium with a lower morphine content. In countries which used to supply the opium smoking market, manifold incisions of the capsules were profitable, since more opium could thus be obtained. This opium is at the same time more suitable for smoking because of its lower morphine content. Yugoslav opium has an unpleasant taste and a high morphine content and has therefore never been in demand on the smokers' market nor exported for this purpose. It is intended only for the Western market, where morphine content is in demand. Accordingly, manifold incision of capsules is not profitable. The fact that the capsules are cut only once accounts for the considerably greater output of opium per hectare in Far Eastern countries than in Yugoslavia.

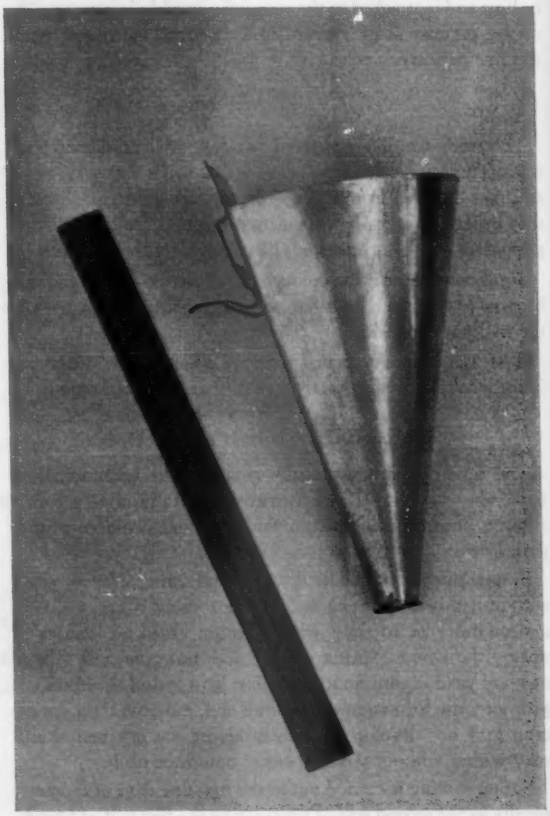

FIGURE 4

Vessel for collecting raw opium

Between 0.02 and 0.05 g of opium are obtained from each capsule. The output per hectare varies between 4 and 15 kg, according to the place and year.

Raw opium contains from 25% to 35% moisture, and the "Bilka" enterprise, which is the only one authorized to purchase opium, subjects it to further drying and standardization in preparation for the domestic trade and export.

About three weeks after the opium harvest, the plant becomes fully ripe and the capsules are collected and broken up for the seeds, which are used to manufacture oil. Between 300 and 400 kg of seeds are obtained per hectare, according to the place and year. 100 kg of seed usually yields from 45 to 48 kg of edible oil.

Advantages and Risks of Cultivation

The cultivation of the opium poppy is highly profitable and, at the same time, very risky for the producer. One advantage is that nearly the whole plant can be used. Opium and poppy seeds are commodities for which there is always a market. The relatively high value of these products in relation to their volume is a highly favourable factor for producers in parts of the country with poor communications. Continuous contact with the outlet, which is essential, for example, in market gardening, is not required in this case, and opium can be kept for a long time without any danger of deterioration in quality (storage leads to a decrease in the moisture, but the amount of morphine remains unchanged). The seed cakes left after the oil has been extracted are used as cattle food, the dry capsules are sold as raw material for the production of alkaloids and the remaining straw is used as litter and as fuel to replace wood (a large proportion of the opium region is poor in timber). The relatively quick growth of the plant often makes it possible to use the soil for yet another crop in the same season, while the early harvesting of opium gives the producer his first income of the year. The main cultivation operations take place at a time when no other agricultural work has to be done. Finally, some kinds of soil are suitable only for cultivating the opium poppy and yield considerably less of any other crop.

On the other hand, this is one of the agricultural crops exposed to the greatest risks, which persist throughout the growing period of the plant.

Sowing takes place in the autumn, after the first autumn rains moisten the earth. If these rains fall too late, the plant is insufficiently developed by the winter, and is therefore sensitive to cold and may be destroyed even in a mild winter. Another risk of crop failure is that of a hard winter, especially without snow. An unduly mild winter is also unsuitable, for the plants can develop too fast and the opium-gathering period may occur too early, when rains are more frequent. A wet spring can promote the development of plant diseases to which the poppy is very sensitive and too much moisture in the ground makes the latex too thin and causes it to trickle out of the capsule on to the ground after incision. The chief danger of the producer, however, is rain at the time of the harvest, as the harvest can be potsponed for only a few days. Rain during the night following the incising of the capsules may entirely wash away the drops of latex and completely destroy the crop. Even dew can cause serious damage at that period.

In the case of spring cultivation, there is the further risk of dry weather setting in before the plants are sufficiently developed, so that they may wither without yielding either opium or seeds.

The opium poppy is one of the most intensive agricultural cultivations and requires a great deal of manpower; the poppy needs constant care throughout its period of growth. Approximately 30 days of team work and 260 manpower days (including collection of opium and seeds) are required to cultivate one hectare (7). It should also be borne in mind that the incision of the capsules and collection of the opium are operations requiring many specially trained workers in the relatively short period suitable for the harvest. A shortage of specialized labour at harvest-time is yet another risk to which the cultivation of the opium poppy is exposed.

The hazards of opium poppy cultivation may best be seen from table 1.

TABLE 1

Opium production in Macedonia, 1929-1937

Year	Area in hectares		% of sown area harvested	Output	
	Sown with poppy	Harvested		Opium kg	Seed kg
1929...	5 528	1 622	29	9 820	636
1930...	14 110	12 048	91	70 410	16 526
1931...	10 913	8 690	80	58 730	10 649
1932...	4 009	569	14	2 500	445
1933...	5 343	4 251	80	26 360	7 472
1934...	6 476	5 858	91	44 390	10 463
1935...	8 035	7 456	93	60 620	10 380
1936...	8 973	7 826	87	63 220	20 795
1937...	8 310	7 430	89	62 200	25 406
Average	7 966	6 196	78	44 250	11 419

It may be noted that in 1935 93%, whereas in 1932 not more than 14% of the sown area was harvested. While 70,410 kg were produced in 1930, only 2,500 kg were produced in 1932.

The mechanization of agriculture cannot make the production of opium much cheaper. Apart from ploughing, sowing and winnowing the seeds (with ploughs, seeders and winnowers) the remaining operations can be performed only by human hand. Labour takes up from 80 to 90 per cent of the production costs (9).

From above it is evident that opium is not suitable for large state or co-operative farms, using modern agricultural techniques, nor for large areas in general. However, the opium poppy is being cultivated also on state and co-operative farms, but over relatively small areas, as well as on individual farms.

From 1948 to 1957, the following areas of Yugoslavia were sown with poppy (average areas are given) (10).

	Hectares
On state farms	68
On co-operative farms	432
On private farms	4,270

The Delivery and Control System

General provisions on control over the production, manufacture and processing of and trade in narcotic drugs are contained in the Act on Narcotic Drugs of 23 January 1950.

Raw opium may be produced only in authorized areas. Every year, each producing district announces the total areas sown with opium poppy, on the basis of production authorization issued to the producers.

The producers may be state farms, co-operative and individual rural households.

In any given year, the producers are bound to turn over the total amount of raw opium they have produced to the " Bilka " enterprise at Skopje, which alone is authorized to purchase it. Any producer who does not do so or who sells raw opium to unauthorized persons is liable to criminal prosecution.

Control over sown areas and the quantities of raw opium put up for sale is effected by the local authorities, who, surveying the sown areas, can also estimate the amount of opium obtained, although it varies widely from one district to another according to weather conditions. The fact that a large number of people, mostly neighbours and local inhabitants, must take part in incising the capsules and collecting the opium makes it much more difficult to conceal the opium obtained.

Every year before sowing, the producers may make an agreement with " Bilka " in advance, for an interest-free loan in fertilizers or in cash, on condition that the loan will be converted when the crop is purchased. Moreover, the purchase price is guaranteed in advance for the producers, expressed in morphine units.

This compulsory purchase is effected at different times in different places. The day when opium is to be purchased at a given place is announced in advance. The purchase is carried out by a commission consisting of three members, one of them an expert of " Bilka " and another a representative of the local authorities.

Should the judgement of the producer and of the commission or one member of the commission concerning the quality of the opium (morphine content) fail to coincide, either side is entitled to ask that a chemical analysis should be made. The cost of the analysis is borne by the side whose appraisal is proved to be wrong.

Experts can estimate the morphine content with reasonable accuracy. According to the charateristics of opium in individual districts and according to its consistency, colour, smell and even taste (bitterness), they can make estimates which in the majority of cases differ from the chemical analysis by less than 1%. Experience has shown, however, that even they can make considerable errors; no estimate whatsoever can be regarded as absolutely reliable.

" Bilka " exports opium and supplies it to wholesale pharmaceutical firms and to the only Yugoslav alkaloid factory, " Alkaloid ", at Skopje. " Alkaloid " exports alkaloids and supplies them to wholesale pharmaceutical firms.

All commercial firms and factories authorized to deal in narcotic drugs, as well as pharmacies and hospitals, have to keep special registers of their trade in narcotic drugs. Delivery vouchers, doctors' prescriptions and hospital vouchers (for hospitals and pharmacies) serve as the documents on the basis of which the register of narcotic drugs is kept. The register has numbered pages, and is controlled and stamped by the authorities, who affix the control ribbon and seal which make it impossible to alter the entries.

The control system is greatly facilitated by the fact that there are no private trade enterprises or factories in Yugoslavia and no private pharmacies and health institutions.

Within the Federal Administration for Pharmaceutical Service and Medical Supplies there is a Commission on Narcotic Drugs, consisting of the representatives of federal institutions interested in the problem of opium and narcotic drugs. The Commission's task is to co-ordinate the work of the interested departments by enforcing the provisions of the Act on Narcotic Drugs, applying laws and regulations on narcotic drugs and carrying out the obligations arising from conventions and other international instruments.

Within the Committee for Foreign Trade there is an Opium Office which controls the import and export of narcotic drugs and issues import and export licences.

Some Characteristics of Yugoslav Opium

Yugoslav opium is put on the market in the form of hard bricks, 2 to 2.5 cm thick, 6 to 7.5 cm wide and 18 to 20 cm long, packed in cases lined with tinplate. Each brick bears the print of a thrice-incised poppy capsule and the inscription " Bilka ", Jugoslavija (see figure 5).

Figure 5

Trade mark printed on each piece of opium-brick

The opium is granulous when broken, dark reddish-brown in colour, with a characteristic smell and an acrid, unpleasant and very bitter taste.

Under the microscope very few plant particles can be seen (particles of capsule and leaf) and under the polarizing microscope a preponderance of small crystals, with a few square grains and sometimes a few rods are visible (11). The opium is similar to Turkish opium in microscopic appearance.

Yugoslav opium has the highest morphine content in the world (12). The morphine content calculated in dehydrated opium is more or less constant and varies between 15.9% and 17.2% (13). Analytical data on the content of other important alkaloids are scanty; however, the analyses of various laboratories have shown contents of 0.9 to 1.6 per cent of codeine,

2.9 to 7 per cent of narcotine, 0.7 to 1.7 per cent of thebaine and 1.2 to 3.3 per cent of papaverine (14).

The most characteristic property which distinguishes Yugoslav opium from other opiums is its typical ultra-violet absorption spectrum (15). This property is mostly attributed to a constant ratio between the content of thebaine and papaverine in this opium. According to the ratio between these two alkaloids, Yugoslav export (Macedonian) opium, unlike the majority of the Asian types, distinctly falls into the papaverine type. Similar results (to a certain extent) are obtained in the case of Greek opium and some Turkish types. It is interesting to note that the opium which has been grown on an experimental basis in northern Croatia is quite different (16) and belongs to the thebaine type.

Another characteristic is the composition of the ash content (17).

It has also been found that the quantity of yellow pigment in Yugoslav opium increases constantly and steadily as it grows older, a fact which can be used as an approximate assessment of its age (18).

Poppy capsules

In recent years, poppy capsules (together with poppy straw) have gradually been replacing opium as raw materials for the production of alkaloids. Dried and crushed capsules are mainly used, together with approximately 10 cm of the stem under the capsule.

In suitable soil, the highest morphine content is found in ripe capsules, while in poor soil it is found in capsules which are not quite ripe (5). The highest morphine content (1.25%) is found in capsules from the neighbourhood of Kavadarci (5), while the content found in other parts of Macedonia varies between 0.47% and 1.05% (19).

The morphine content of incised capsules from which the opium has been taken is 40% to 60% less than that of unincised ones.

The stems 10 cm from the top have a morphine content of 50% to 70% less than the capsule, although in some cases it has been found to be the same as that of the capsule (19).

Producers and Production Prospects

As already stated, the cultivation of the opium poppy is extremely intensive and labour represents between 80% and 90% of the production costs. Accordingly, in the period before the Second World War, a clear distinction could be made between two categories of producer. One of these categories consisted of town dwellers (contractors, landowners, tradesmen, traders, etc.) who cultivated the opium poppy on land owned or rented by them, using hired labour for all the operations.

When labour was relatively cheap, this form of production was in most cases profitable. However, in periods when the price of opium on the world market fell considerably, these producers used to abandon opium cultivation and turn to other profitable but less risky crops.

Thus, for example, the vertiginous fall in prices in 1930 and 1931 (between January 1930 and December 1931, the world prices of opium fell to one-sixth), led to a decrease in the area sown from 14,110 hectares (1930) and 10,913 hectares (1931) to 4,009 hectares in 1932. After this crash, the producers' confidence in this crop returned very slowly, which will be seen from the gradual increase of sown areas to some 5,000, 6,000 and 8,000 hectares in the following five years (see table 1).

The second category of producers consisted and still consists of rural small-holders, owning very small plots of land worked by their own labour and that of members of their household. Since these small undertakings do not use or use very little hired labour, their production costs are quite differently distributed. The cost of labour does not mean much to them: it is far more important to be able to use household labour at a time when there are usually no other operations to be performed on the land. Moreover, such farmers are often tied to opium poppy cultivation by the fact that their land would yield much less of any other type of crop. These are producers who therefore remain faithful to the opium poppy and on whom fluctuations of world prices have considerably less effect.

The large-scale public works which were undertaken in the People's Republic of Macedonia in the post-war years (hydro-electric power stations, roads, factories), the industrialization of the country, mechanization and certain technical measures in agriculture have resulted in a gradual rise in the standard of living and consequently in a rise in the cost of labour. As labour is a predominant factor in production costs, the new conditions do not promote the development of opium production. Mechanization, irrigation and other technical measures in agriculture have made some other crops more profitable and have made it possible to cultivate other areas which were hitherto suitable for the opium poppy only. The large-scale public works have attracted a considerable amount of labour from the country and have concentrated it near the building sites, while the industrialization of the country is gradually turning villagers, especially the poor ones, into industrial workers. In some villages this has led to a decrease in the skilled labour which is essential at the time of the cutting of the capsules and collection of the opium, so that over considerable areas the capsules remained unincised and no opium was obtained, or the incisions were made by unskilled labour, which resulted in a decrease of the yield.

In its history, Macedonia has often been the scene of armed conflicts during which the value of money fell overnight. Opium, on the other hand, has always been a stable " currency ", the real value of which remains constant. Macedonian villagers therefore got into the habit of keeping opium as a " gold reserve " which is sold only in case of need. Thus it became a tradition among the villagers to keep opium for ten or more years as a dowry for their daughters.

This old custom of keeping opium instead of money was resumed during the Second World War and the occupation period. Opium became again the only stable currency. No serious control measures were undertaken and the opium

was kept in the houses of many of the producers. After the liberation of the country measures were again taken on the basis of the Act of December 1938 for selling all the opium produced through one enterprise. These measures, which were further strengthened by the Act on Narcotic Drugs of 23 January 1950, have been most positive from the point of view of suppression of illicit traffic, but have decreased the interest of producers in cultivating opium. As a result of these measures, opium has ceased to be the household " gold reserve ".

In addition, the loss of the 1949 crop as the result of bad weather (only 540 kg of opium was obtained from the 7,000 hectares sown) and the favourable prices of certain other crops (e.g., tobacco) in post-war years make it even easier to understand the falling off of interest in opium production.

Whereas the sown area before the war was about 8,000 hectares, yielding approximately 45 tons of opium (see table 1), the area over the last five years has been approximately 5,000 hectares, yielding about 25 tons of opium (see table 2).

TABLE 2

Opium production in the People's Republic of Macedonia, 1955-1959

Year	Area in thousands of hectares		Opium yield	
	Sown	Harvested	Total in tons	kg per hectare
1955	4.9	4.7	26.9	5.7
1956	5.1	4.7	27.9	5.9
1957	5.4	2.2	15.4	7.0
1958	5.0	2.0	18.4	9.2
1959 *....	4.2	4.1	31.9	7.9
Average ..	4.9	3.5	24.1	7.1

* The 1959 data of the statistical office of the People's Republic of Macedonia were collected before the completion of the harvest and cannot be considered final.

Although opium production is very likely to increase gradually, because producers are overcoming the aforementioned difficulties, there is little prospect that production will reach the pre-war level, since the basic condition, excess of cheap labour, is lacking.

With regard to the area sown, however, there is every prospect that it will increase considerably, not for the collection of opium, but for obtaining poppy capsules as raw material for the extraction of alkaloids.

While opium production is closely connected with a poor rural economy, the cultivation of the opium poppy for obtaining capsules is suitable for large state and co-operative farms. If the opium is not collected it is possible to sow the plants more thickly and to use mechanical methods of cultivating and harvesting, which will lead to a considerable rationalization of production. Some first steps in this direction are being contemplated.

PRODUCERS AND DRUG ADDICTION

Drug addiction does not exist as a social problem in Yugoslavia. It is limited to a very small number of people in the large towns, mostly intellectuals and health staff who have lived abroad and have become addicts, as well as people to whom the former have directly or indirectly transmitted this evil habit. More cases of drug addiction have been registered in the northern part of the country (Zagreb, Belgrade) than in Macedonia.

Drug addiction is practically unknown among the producers themselves. Some of them know that medicines are made from opium, while some others only know that it is a product which can always be sold.

There are old people who remember cases of " opium eating ", not among the direct producers, but among land-owners and dealers in opium.

It is difficult to explain the fact that in a country where the cultivation of the opium poppy is a centuries-old tradition there is no drug addiction among the direct producers. This may be explained by the fact that the poor Macedonian peasant has always been in the habit of sending the best and costliest products of his land to the market and keeping only the worst and the cheapest for himself. On the other hand, although the level of living of the Macedonian peasant has always been low by European standards, it has never been so low as to force him to seek an escape from his complete misery in drug addiction, as is often the case in certain Asian countries.

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Human pharmacology and addiction liabilities of phenazocine [1] and levophenacylmorphan [2] [3]

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Interest in the addictiveness of phenazocine [4] and levophenacylmorphan [5] was aroused because both drugs were found to be more potent analgesics in mice (11) and man (4, 14, 10, 13) than morphine, but were far less potent than morphine in reducing the intensity of abstinence from morphine in addicted monkeys (3). Thus, it seemed possible that a considerable dissociation in analgesic and abstinence-suppressing potencies (sometimes equated with "addiction liability") had been achieved in these drugs. Studies on the human pharmacology, with particular emphasis on the addictiveness of both drugs, were therefore undertaken.

Methods

Drugs. — Drugs were given hypodermically, except that single doses of NIH-7519 and NIH-7525 were also evaluated by the intravenous route. NIH-7519 and NIH-7525 were dissolved in 25% propylene glycol in water in a concentration of 0.4 to 1%. Use of propylene glycol was necessary because of the low solubility of the drugs in water. Placebo consisted of the vehicle used to dissolve the drugs. Morphine sulfate was dissolved in distilled water to make a 2 to 5% solution. Weights of the drugs refer to the salts.

Subjects. — All subjects used in these experiments were males who were serving sentences for violations of the federal narcotic laws, and who volunteered for the experiments. All were physically healthy, and none presented evidence of the major psychoses. Those patients used in assessing the effects of single doses and in direct addiction experiments were abstinent from opiates (non-addicted, non-tolerant "former" addicts) at the time the experiments were begun.

Experiment 1. — Effects of Single Doses Subcutaneously

In preliminary experiments it was found that 2 to 3 mg of NIH-7525 and 3 to 4 mg of NIH-7519 induced subjective, behavioural and objective effects comparable to those caused by 20 mg of morphine subcutaneously. An experiment was then designed in which 12 to 17 subjects, who were unaware of the identity of the agents, received in a randomized fashion the following medications: placebo (16 patients); 2 and 3 mg of NIH-7525 (17 patients); 3 and 4 mg of NIH-7519 (17 patients); and 8 mg (12 patients), 13 mg (17 patients), and 20 mg (16 patients) of morphine. The inequalities in the numbers in the various groups were due to expiration of eligibility of some of the patients for participation in experiments before all the doses could be completed.

Immediately prior to and at hourly intervals after injection of the drugs, the diameter of the patients' pupils was measured in a dark room under conditions of controlled light and accommodation by comparing the size of the pupils with blackened circles of known diameter on a card. The patients remained in a special ward throughout the experimental period, and were observed by specially trained aides. Immediately before and at hourly intervals after administration of the drugs, the patients completed, with the help of aides, a simple questionnaire consisting of the following questions: "I feel the medicine;" "The feeling is like: morphine, marihuana, benzedrine, heroin, barbiturates;" "I don't feel anything;" "I am nervous;" "I am relaxed;" "I am nauseated;" "I am sleepy;" "I have a drive;" and "I would like more." The aides also filled out a questionnaire dealing with observable changes in behaviour which frequently occur after morphine and wrote supplementary notes as indicated.

The data were analysed in the following ways: Change in the size of pupil was obtained by subtracting the post-drug values from the pre-drug values. The area under the time-action curve composed of these changes in pupillary diameter was calculated by the method of Winter & Flataker (15), thus converting all the data on a particular patient for a particular dose of a drug to one figure. Means and standard errors were calculated by standard statistical techniques. In addition, the mean change at each hour after administration of the drug was calculated in order to obtain time-action curves for the various doses of the different drugs.

The responses on the questionnaire were classified as follows: A response that the subjective effects were similar to morphine or heroin at any time during the observation period was scored "positive for opiates"; a response that the effects were similar to amphetamine, barbiturates, or marihuana was scored "positive for other drugs"; a response that subjective effects were present which were not regarded as similar to those of any drug listed in the questionnaire was scored "questionable"; denial of all subjective effects was scored "negative". It was hoped that the responses classified in this way could be used to deter-

[1] *dl*-2'-Hydroxy-5,9-dimethyl-2-(2-phenethyl)-6,7-benzmorphan HBr, NIH-7519.

[2] *l*-3-Hydroxy-N-phenacyl-morphinan methane sulfonate, NIH-7525.

[3] Observations reported in this article were taken into account by the WHO Expert Committee on Addiction-producing Drugs at its tenth session, in October 1959, when considering the question of international control of the drugs phenazocine and levophenacylmorphan (see, at the end of this volume, "Note: Changes in the scope of control").

[4] Phenazocine was prepared in the laboratories of Smith, Kline & French according to the method devised by Dr. Everette L. May of the National Institutes of Health. The Smith, Kline & French code number is SKF-6754. The drug will be referred to throughout the paper by the code number of the National Institutes of Health, NIH-7519.

[5] Levophenacylmorphan was supplied through Dr. Nathan B. Eddy by Hoffman-La Roche, Inc., Basle, Switzerland, under the code number Ro 4-0288-1. The drug will be referred to throughout the paper by the code number NIH-7525.

mine the " euphoric " potency of NIH-7519 and NIH-7525 by probit analysis, using " positive for opiates " as the primary criterion of the response; but, as will be seen in the results, the doses of NIH-7519 and NIH-7525 chosen were too high to yield good estimates by this method, so another method of analysis was tried. The total number of responses scored positively on the questionnaire (excluding responses to the questions " I don't feel anything " and " I would like more ") which were not scored positively before the drug were counted and the mean number of responses was calculated for each dose of each drug.

The means for the total number of questions and the areas under the curves for pupillary constriction were used in constructing dose-effect curves. Regression lines for these curves, relative potencies of NIH-7519, NIH-7525 and morphine, and 95% confidence limits were calculated by the methods described by Bliss (2).

Experiment 2. — Effect of Single Doses Intravenously

NIH-7519 was administered intravenously in a dosage of 2 mg (3 patients); 3 mg (5 patients); and 5 mg (9 patients). NIH-7525 was given intravenously in a dosage of 0.5 mg (7 patients); 1.0 mg (10 patients); and 1.5 mg (4 patients). Some patients received both drugs, and some different dosage levels of the same drug. There was no comparison of effects of morphine given intravenously in the same subjects. The primary object of the experiment was to ascertain if an intravenous dose of both NIH-7519 and NIH-7525 could be given that would induce subjective and behavioural effects in post-addicts comparable to that of 20 to 30 mg of morphine sulfate similarly given. The questionnaire referred to under subcutaneous doses was completed at hourly intervals for eight hours after both drugs were given, and behaviour and pupillary diameter were concurrently recorded. Since, from the standpoint of abuse, the important points to be ascertained were similarity of the unknown drug to morphine or heroin and the intensity and duration of its effect, emphasis was placed on these aspects in tabulating the data (table 3).

Experiment 3. — Twenty-four-hour Tests for Ability to suppress Symptoms of Abstinence

Five patients who were addicted to and stabilized on 240 mg of morphine daily (divided into four doses) were used in these experiments. In each test, each patient received his last dose of morphine at 4 p.m., and was given no more morphine until 4 p.m. on the following day. During this period, each patient would normally receive three doses of 60 mg of morphine. Tests were conducted at weekly intervals with patients being returned to their accustomed doses of morphine between tests. The patients were not aware of the identity of the drugs under test. Each patient received in randomized fashion during various substitution periods a total dosage of 3, 6, and 9 mg of NIH-7519 and NIH-7525. Each dosage was divided among three equal doses. For comparison, data were available on 9 other patients who received in similar tests 18 mg (10 per cent of their usual dosage of morphine), 36 mg (20 per cent), and 90 mg (50 per cent) of morphine instead of the 180 mg of morphine they normally would have been given during the substitution period. Observations for symptoms of abstinence were made hourly from the fourteenth to the twenty-fourth hour (6 a.m. to 4 p.m.) after the last dose of morphine, and hourly point-scores of the intensity of abstinence calculated according to the system of Himmelsbach (8). The areas under the time-action curves composed of the hourly point-scores were calculated by the method of Winter & Flataker (15), yielding area figures (points multiplied by hours) termed " point-hour " scores. The mean figures for the various doses of NIH-7519, NIH-7525 and morphine were used in constructing dose-effect curves. Regression lines, relative potencies, and 95% confidence limits were calculated according to the methods described by Bliss (2).

Experiment 4. — Substitution for Morphine for Ten Days

Five patients who were addicted to and stabilized on 240 mg of morphine daily were available for these experiments. In two cases, morphine was abruptly discontinued, and 32 mg of NIH-7519 daily (divided into four doses subcutaneously) was substituted for the morphine. In the other 3 patients, 24 mg of NIH-7525 daily was substituted for morphine. The dosages of NIH-7519 and NIH-7525 were chosen on the basis of the potencies of the drugs in suppressing abstinence from morphine in the 24-hour substitutions. After ten days of substitution, NIH-7519 and NIH-7525 were replaced with placebo injections. Throughout the phases of stabilization on morphine, substitution of NIH-7519 and NIH-7525, and abrupt withdrawal of the latter, observations for symptoms of abstinence were made three times daily, and the intensity of abstinence calculated in terms of daily point-scores according to the system of Kolb & Himmelsbach (9). The area under the time-action curves for the first seven days following abrupt withdrawal of NIH-7519 and NIH-7525 was calculated, yielding a figure termed the TAS-7 (total intensity of the abstinence syndrome for seven days). The daily dosages of morphine corresponding to the TAS-7 scores for the individual scores were interpolated from the curve of Andrews & Himmelsbach (1), which relates the intensity of abstinence from morphine, as reflected by the TAS-7 scores, to the daily dosage of morphine. In this way, a rough comparison of the intensity of abstinence following withdrawal of the substituted drugs with the intensity of abstinence after withdrawal of equivalent amounts of morphine can be made.

Experiment 5. — Preliminary " Short " Direct Addiction Experiments

These experiments were performed in order to obtain a preliminary idea of whether NIH- 7519 and NIH-7525 would produce physical dependence in man. One patient received NIH-7519 for 19 days with the daily dosage increasing as rapidly as tolerated, from 5 mg on the first day to 34 mg on the 19th day. Another patient received NIH-7525 for 19 days, the daily dosage increasing from 5 mg on the first day to 28 mg on the 19th day. Withdrawal of the drugs was abrupt and complete. Observations for symptoms of abstinence were made, and daily point-scores calculated according to the system

of Kolb & Himmelsbach throughout the experiment, and for ten days after withdrawal of the drugs. Precipitation of abstinence by subcutaneous administration of 5 mg of nalorphine was attempted on the 16th day (NIH-7519) and 17th day (NIH-7525) of chronic drug administration, with observations for symptoms of abstinence being made at intervals of 15 minutes twice before and four times after the administration of nalorphine.

Experiment 6. — " Long " Direct Addiction to NIH-7519

One patient received NIH-7519 in dosages increasing from 5 mg daily (divided into four equal doses) to 60 mg daily on the 69th day. This level was maintained until the 127th day, after which NIH-7519 was replaced with placebos. A preliminary short withdrawal lasting 42 hours was carried out on the 24th to the 26th day, after which the patient was returned to the drug. Prior to this short period of withdrawal, the patient had attained a dosage of 24 mg daily, and when the drug was resumed he was begun on 24 mg daily. On the 18th day of addiction, when the patient was receiving 24 mg of NIH-7519 daily, abstinence was precipitated by the subcutaneous administration of 5 mg of nalorphine. Observations for symptoms of abstinence were made three times before and four times after (at intervals of 15 minutes) administration of the nalorphine. On the 77th day of addiction, when the patient was receiving 60 mg of NIH-7519 daily, a second nalorphine test was carried out, using a dose of 2 mg subcutaneously. Throughout the addiction period, and for 15 days after withdrawal of NIH-7519, observations for symptoms of abstinence were made three times daily. Daily point scores were calculated by the method of Kolb & Himmelsbach (9).

Experiment 7. — " Long " Direct Addiction to NIH-7525

An experiment analogous to that employed in the above " long " NIH-7519 test was used for evaluating NIH-7525. The starting dose was 4 mg daily, with a comparable increase in dosage. It was planned to continue the chronic administration of NIH-7525 for 100 days, but after 26 days the subject requested that he be allowed to withdraw from the experiment, and no further drug was administered. A maximum dosage of 26 mg divided among four equal doses was attained on the 23rd day, and this was continued through the 26th day. Observations for intensity of abstinence (9) were made for ten days, beginning on the 27th day of the test. Precipitation of abstinence with nalorphine was not attempted.

Experiment 8. — " Short ", " Double-blind " Addiction Tests with Morphine and Placebo Controls

Eight patients served in these experiments, which were designed to determine whether a " short " direct addiction test could be used to assess the addictiveness of new drugs employing morphine and codeine as the standards for comparison. The patients received the following medications in randomized order for periods varying from 19 to 20 days: placebo (capsules of starch flavoured with quinine, orally); codeine sulfate in capsules, increasing from 200 mg to 1,500 mg daily; morphine sulfate in capsules, increasing from 40 to 240 mg daily; ethyl-4-phenyl-1 (3-cyano-3, 3-diphenylpropyl)-4-piperidine carboxylate HCl (R-1132) in capsules, increasing from 40 to 300-480 mg daily; *d*-3-methoxy-N-phenethylmorphinan in capsules, in doses increasing from 180 to 1,200 mg daily; morphine sulfate subcutaneously, increasing from 32 to 240 mg daily; NIH-7519 subcutaneously, increasing from 4.8 to 12-36 mg daily; and NIH-7525 subcutaneously, increasing from 4.8 to 24-36 mg daily. Only the data obtained with the placebo, morphine subcutaneously, NIH-7519 and NIH-7525 are pertinent to this report. The higher maximal dosages for NIH-7519 and NIH-7525 were those in the original design. These dosages, however, proved to be more than the first patients who received these amounts could safely tolerate, so the maxima were reduced to 24 mg daily in the case of NIH-7525. Unfortunately, all patients had completed addiction to NIH-7519 before this change in the dosage schedule was made. The identity of the drugs was known only to one person who prepared the solutions and capsules, and issued them in coded bottles. Drugs were withdrawn by substituting placebo capsules or injections appropriate to the drug being given. The person in charge of the drugs also decided on which day (19th-20th) drugs would be replaced by placebos. Withdrawal periods lasted ten days, after which the patient began another round of chronic drug administration.

Observations were made three times daily. These included rectal temperature, respiratory rate, pulse rate and blood pressure. Caloric intake was measured daily. Body weight was recorded at 6 a.m. daily. In addition, hours of sleep, hours of inactivity (lying horizontal on bed), initiative activity (hours off the ward) were recorded at half-hour intervals daily. Prior to starting the experimental regimen, control observations, including those mentioned above, were carried out for three days in order to accustom patients to all routines. Two complete blood counts and two urinalyses (including a test for bile) were made during this interval. Blood counts and urinalyses were made at intervals of three weeks thereafter.

Throughout the experiments, observations for symptoms of abstinence were made according to the procedures of Kolb & Himmelsbach (9). Daily point-scores were calculated according to the method of the same authors, using the averages for respiratory rate, blood pressure, and temperature during the last seven days on the drugs (standard, Himmelsbach). In addition, other scores were calculated, using the means of the measurements during the period in which placebos were administered for 30 consecutive days (modified, Himmelsbach). The areas under the time-action curves for ten days of abstinence (TAS-10s) were calculated by the method of Winter & Flataker (15) for the respective drugs and methods of scoring. Differences in the TAS-10 scores between morphine, NIH-7519, and NIH-7525, and between all three drugs and placebo were scored by the " t " test for paired observations (5). In this method of analysis, each patient served as his own control. The differences in the daily point scores obtained by both methods of scoring on the second and third days of abstinence were also evaluated by the " t " test for replicated data.

At 7 p.m. on each day of the experiment, each patient completed a questionnaire dealing with the subjective effects

of the drug he was receiving, and concurrently a separate questionnaire dealing with the behavioural changes observed was completed by an aide. The method is being described in detail elsewhere (7).

Results

Experiment 1. — Effects of Single Doses Subcutaneously

The data on the subjective effects of morphine, NIH-7519 and NIH-7525 are presented in table 1.

Table 1

Subjective effects after morphine, NIH-7519 and NIH-7525

Drug	Dose (mg)	Number of study subjects	Number of patients responding [a]				Average total responses [b]
			Positive, opiates	Positive, other drugs	Questionable	Negative	
Placebo	—	16	0	0	0	16	0.4
Morphine	8	12	4	[1]	5	3	7.2
Morphine	13	17	12	0	4	1	15.4
Morphine	20	16	14	1 [1]	1	0	23.7
NIH-7525	2	17	12	0	4	1	15.4
NIH-7525	3	17	15	0	0	2	19.8
NIH-7519	3	17	10	[1]	4	3	12.0
NIH-7519	4	17	10	1	3	3	15.5

[a] For method of scoring, see text. Figures in brackets represent patients who also scored effects positively for opiates.

[b] These figures are the averages of the total number of positive responses over the eight-hour period described in the text.

With respect to classification of the questionnaires as "positive for opiates", it is apparent that the majority of the subjects regarded the subjective effects of doses of both NIH-7519 and NIH-7525 as being similar to those of morphine and heroin. Graded responses were obtained with the various doses of morphine and NIH-7525, but the response to NIH-7519 was flat, 10 of 17 patients responding "positively for opiates" on both doses. From the data, it seems that 2 mg of NIH-7525 and 3 mg of NIH-7519 are roughly equivalent to 13 mg of morphine. With respect to the total number of questions, graded responses were obtained with all three drugs. The dose-effect curves constructed from the mean number of positive responses are shown on the right side of figure 1. The relative potencies calculated from these curves with 95% confidence limits were: 1 mg of NIH-7519 equals 3.25 (2.32-4.25) mg of morphine, and 1 mg of NIH-7525 equals 6.11 (5.04-7.46) mg of morphine in inducing subjective effects. These curves met the usual tests for slope and parallelism. The dose-effect curves constructed from the means for total pupillary constriction appear on the left side of figure 1. The remarkable parallelism of these curves with those obtained with the total questions should be noted. The calculated relative potencies in constricting the pupil within 95% confidence limits were: 1 mg of NIH-7519 equals 3.81 (1.27-5.64) mg of morphine, and 1 mg of NIH-7525 equals 5.2 (2.74-7.95) mg of morphine. The agreement between the two estimates of potency for both NIH-7519 and NIH-7525, one derived from a subjective measurement (total

Figure 1

Dose-effect relationship and relative potency for pupillary constriction and subjective responses with NIH-7525, NIH-7519 and morphine. Single doses were administered subcutaneously to non-addicted, non-tolerant former addicts.

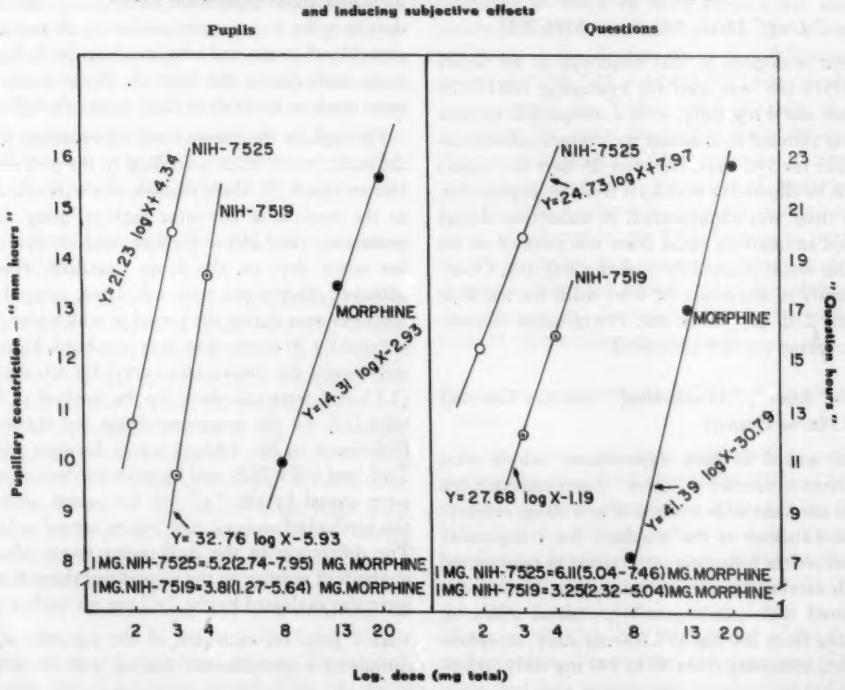


TABLE 2

Average change from control in pupillary diameter in patients receiving morphine, NIH-7525 and NIH-7519

Drug	Dose (mg)	Number of study subjects	Hour after drug [a]								Total [b] "mm hours"
			1	2	3	4	5	6	7	8	
Placebo	—	16	0.03	0.0	0.06	0.09	0.03	0.16	0.03	0.04	0.45 ± 0.17
Morphine	8	12	1.0	1.4	1.5	1.4	1.4	1.3	1.2	1.0	9.96 ± 1.28
Morphine	13	17	1.6	1.9	1.9	1.9	1.8	1.7	1.6	1.4	13.4 ± 1.35
Morphine	20	15	1.8	2.1	2.2	2.2	2.27	2.2	2.0	1.7	15.7 ± 2.0
NIH-7525	2	17	1.6	1.9	1.80	1.6	1.30	1.0	0.9	0.8	10.7 ± 1.4
NIH-7525	3	17	2.0	2.3	2.3	2.1	1.9	1.7	1.6	1.5	14.5 ± 1.55
NIH-7519	3	17	1.3	1.5	1.6	1.4	1.3	1.1	1.1	0.8	9.7 ± 1.4
NIH-7519	4	17	1.7	2.1	2.2	2.0	1.8	1.6	1.7	1.5	13.8 ± 6.1

[a] All figures represent mean change (decrease) in mm at the particular hour indicated.
[b] These figures are the means plus or minus standard errors of the area under the time-action curves.

responses on the questionnaire) and the other from an objective measurement, is rather astonishing. The lack of any significant response to placebo should also be noted. The time-course of action of the various doses of the three drugs was similar, and is shown in table 2.

The behavioural changes observed after NIH-7519 and NIH-7525 were similar to those seen after morphine, and consisted of increased loquaciousness, increased psychomotor activity in some patients, sedation with alternating somnolence ("nodding") in others, scratching, etc. These behavioural effects occurred even when subjective effects were denied.

TABLE 3

Single doses of NIH-7519 and NIH-7525 given intravenously (subjective identification and effects on pupillary diameter)

Number of subjects	Drug	Dose in mg	Identified as [a]	Maximum pupillary constriction (average, in mm)	Duration of pupillary constriction, in hours [b]
3	NIH-7519	2	1 placebo 1 morphine 1 heroin	2.4	4.5
5	NIH-7519	3	2 placebo 2 morphine 1 heroin	1.9	5.4
9	NIH-7519	5	1 placebo 1 morphine 7 heroin	2.8	6.3
7	NIH-7525	0.5	1 morphine 6 heroin	2.3	3.1
10	NIH-7525	1.0	1 morphine 1 dilaudid 8 heroin	3.00	6.5
4	NIH-7525	1.5	4 heroin	3.5	7.0

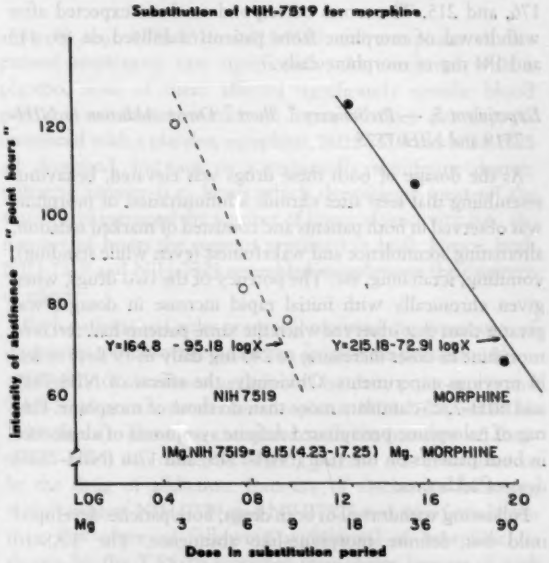
[a] Figures refer to the number of subjects. Designation of specific drugs by all subjects was very definite in these experiments when the drugs were administered intravenously (impressions of subjects are less well crystallised when drugs are given subcutaneously).
[b] Based upon the number of hours for pupils to return to within 1.0 mm of pre-drug status. Observations were extended to 8 hours after drug, and if pupils had not returned to within 1.0 mm of the pre-drug value by then, a value of 8.5 hours was used.

Experiment 2. — Effect of Single Doses Intravenously

The data on the effects of NIH-7519 and NIH-7525 are shown in table 3. It is apparent that both compounds were identified consistently as either morphine or heroin; that the effect was quite intense, as indicated by the marked constriction of the pupil; and that it persisted for a considerable time, as shown by the duration of the pupillary constriction. Although no quantitative figure can be given, since not all of the subjects were used in both experiments, it is estimated that 1 mg of NIH-7525 is two to five times as potent as NIH-7519 when the drugs are given intravenously.

FIGURE 2

Dose-effect curves and relative potency for suppression of abstinence from morphine by NIH-7525 and graded doses of morphine. Twenty-four-hour substitutions in addicted individuals stabilized on 240 mg of morphine per day.



Experiment 3. — Suppression of Abstinence for 24 Hours

Both NIH-7519 and NIH-7525 proved to be potent suppressors of abstinence. The dose-effect curves constructed from the mean point-hour scores are compared with that of morphine in figures 2 and 3. The calculated potencies with 95% confidence limits relative to morphine for suppression of abstinence were: 1 mg of NIH-7519 equals 8.15 (4.23-17.25) mg of morphine and 1 mg of NIH-7525 equals 9.14 (4.78-19.5) mg of morphine. These estimates of potency are higher than those derived from the subjective response and pupillary constriction after single doses in non-tolerant subjects.

Experiment 4. — Substitution for Morphine for Ten Days

Both NIH-7519 and NIH-7525 were completely adequate substitutes for morphine. The daily point-scores during the last week of stabilization on 240 mg of morphine daily ranged between 0 and 8 points. After substitution of 32 mg of NIH-7519 daily, the daily point scores of the 2 patients fluctuated between 0 and 6 points, although one patient had scattered autonomic signs during the first two days of substitution. The point scores in the 3 patients who received 24 mg of NIH-7525 daily ranged between 0 and 7 during the ten days of substitution. Following discontinuation of both NIH-7525 and NIH-7519, definite morphine-like abstinence appeared. The symptoms included yawning, sweating, lacrimation, anorexia, insomnia, elevation of temperature, change in respiratory rate, weight loss, etc. The abstinence syndrome appeared somewhat more slowly than that of morphine, was less severe, and tended to be prolonged. The average TAS-7 score after withdrawal of morphine from patients stabilized on 240 mg daily would, from the data of Andrews & Himmelsbach (1), be expected to be 235 point-days. The TAS-7 scores after withdrawal of NIH-7519 from the 2 patients were 116 and 143. These scores correspond to those expected after withdrawal of morphine from patients stabilized on 55 and 78 mg of morphine daily. The TAS-7 scores after withdrawal of NIH-7525 were 164, 176, and 215. The scores correspond to those expected after withdrawal of morphine from patients stabilized on 99, 113 and 184 mg of morphine daily.

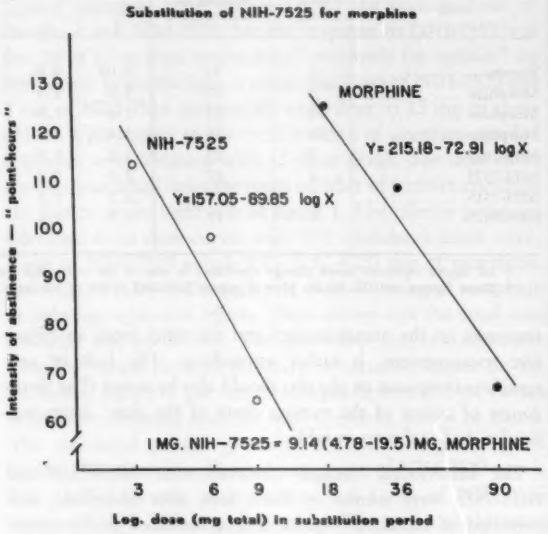
Experiment 5. — Preliminary "Short" Direct Addiction to NIH-7519 and NIH-7525

As the dosage of both these drugs was elevated, behaviour resembling that seen after chronic administration of morphine was observed in both patients and consisted of marked sedation, alternating somnolence and wakefulness (even while standing), vomiting, scratching, etc. The potency of the two drugs, when given chronically with initial rapid increase in dosage, was greater than that observed when the same patients had received morphine in doses increasing to 240 mg daily in 19 days or less in previous experiments. Obviously, the effects of NIH-7519 and NIH-7525 cumulate more than do those of morphine. Five mg of nalorphine precipitated definite symptoms of abstinence in both patients on the 16th (NIH-7519) and 17th (NIH-7525) days of addiction.

Following withdrawal of both drugs, both patients developed mild but definite morphine-like abstinence. The TAS-10 scores (total intensity of abstinence for ten days) were 125.0 after withdrawal of NIH-7519 and 54.0 after withdrawal of NIH-7525. The only data available after withdrawal of morphine after such a short period of addiction appears below in the section on short double-blind direct addiction (experiment 8). The TAS-10 values (scored from standard, Himmelsbach averages) in the 8 patients following withdrawal of morphine in that experiment ranged between 156.5 and 306.0. It should be pointed out that the patient who received NIH-7525 had consistently shown an abstinence syndrome of mild grade in previous studies when opiates were withdrawn abruptly. This is supported by the fact that 8 other patients who received NIH-7525 for a comparable time had TAS-10 scores ranging from 129.5 to 209.0 (see experiment 8).

FIGURE 3

Dose-effect curves and relative potency for suppression of abstinence from morphine by NIH-7519 and graded doses of morphine. Twenty-four-hour substitutions in addicted individuals stabilized on 740 mg of morphine per day.



Experiment 6. — "Long" Direct Addiction to NIH-7519

The patient who served in this experiment developed the same sort of subjective and behavioural changes described above. Mild but definite abstinence was observed after administration of 5 mg of nalorphine on the 18th day of the experiment, and moderate abstinence occurred after 2 mg of nalorphine on the 77th day of the experiment. This patient developed a high degree of tolerance to the drug, as manifested by nearly complete disappearance of the sedative effects before the end of the addiction period, despite the high dosage.

During the 42-hour withdrawal period, on the 24th to the 26th day, the patient did not realize that he was abstinent until 16 hours had elapsed since the last dose of NIH-7519. The abstinence syndrome was quite mild, and by the third day the patient seemed nearly recovered. Following withdrawal on the 127th day, the patient developed severe morphine-like abstinence phenomena, which appeared rather slowly and

declined slowly. The maximum daily point score of 57 was not attained until the 4th day, and the patient still had a score of 29 points on the 15th day of abstinence. The symptoms included the usual autonomic phenomena as well as restlessness, anorexia, fever, hyperpnea, insomnia, and weight loss (15 lb in four days). The TAS-7 score was 304, and corresponds to that expected after withdrawal of morphine from a patient stabilized on 278 mg of morphine daily.

Experiment 7. — " Long " Direct Addiction to NIH-7525

The patient who served in this study developed the same type of subjective and behavioural changes described above in the preliminary trial. However, while his dosage was being progressively increased, he complained intermittently of " gas in the stomach ", nausea, and of being depressed about one hour prior to getting his injection. On the 26th day of chronic drug administration, when he had attained a dosage of 26 mg daily, the patient requested that he be taken off the test, complaining that the drug made him nervous and depressed, and saying, " I don't look forward to anything anymore, not even my next shot. I think about death or a severe illness in myself, such as cancer, or illness in my family." He concluded that if this were the only drug available to him, he would quit drugs entirely. The drug was discontinued abruptly and a moderately severe abstinence ensued.

This patient was called to the ward 20 days after having received his last injection of NIH-7525, and was given 1 mg of this drug intravenously, without knowledge of its identity. He stated it was like dilaudid, and was very pleased with the over-all effects.

Experiment 8. — " Short ", " Double-blind " Direct Addiction

No difficulty was experienced in elevating the dosage of morphine or NIH-7525. All 8 patients attained a daily dosage of 240 mg of morphine by the 18th day of the experiment. The total amount of morphine taken by each patient during the test was 2,644 mg. Two patients who began on NIH-7525 prior to lowering of the maximum dosage to 24 mg daily attained a daily dosage of 36 mg, while 6 who began after the schedule was changed attained a daily dosage of 24 mg. The average total amount of NIH-7525 taken by the patients was 286.2 mg. Difficulty was encountered in elevating the dosage of NIH-7519. As explained in the section on methods, all patients completed this portion of the experiment before the maximum dosage was reduced from 36 to 24 mg daily. Only 3 of the 8 patients attained the full 36-mg dosage. The remaining 5 patients all developed symptoms of excessive drug effects — heavy sedation, nausea, and respiratory depression — so that their dosages were reduced or held at the same level for some days. Under these circumstances,the daily dosages of NIH-7519 attained by 5 patients varied between 12 to 26.4 mg daily, and the average total amount taken by the patients was 327.4 mg. The average daily dosage of NIH-7519 reached by all 8 patients was 25.95 mg daily. This is equivalent to approximately 210 mg of morphine daily in suppressing abstinence. The average daily dose of NIH-7525 attained by all 8 patients was 27 mg. This is equivalent to approximately 247 mg of morphine daily in suppressing abstinence. Throughout the experiment, all 8 patients consistently recognized that the subjective effects of NIH-7525 were similar to those of an opiate. Although all 8 patients reported at some time during the experiment that the subjective effects of NIH-7519 were similar to those of an opiate, as a group they were not as consistent respecting NIH-7519 as they were respecting NIH-7525. Four of the 8 patients identified the subjective effects of NIH-7519 as being opiate-like only occasionally.

The aides, however, consistently reported behavioural changes such as increased loquaciousness, alternating somnolence and sedation (" nodding " or " coasting "), and scratching, throughout administration of both NIH-7519 and NIH-7525. Such behavioural changes were also observed during administration of morphine.

The average effects of NIH-7519, NIH-7525 and morphine as compared with those of a placebo on respiratory rate, systolic blood pressure, rectal temperature, hours of sleep, hours of activity and hours of inactivity are shown in table 4. It is apparent that NIH-7519, NIH-7525 and morphine all depressed respiratory rate significantly. As compared with a placebo, none of them affected significantly systolic blood pressure, rectal temperature or hours of sleep per day. As compared with a placebo, morphine, NIH-7519 and NIH-7525 all depressed, but not to a statistically significant degree, initiative activity (i.e., hours which the patients spent off the ward), and increased the number of hours of inactivity (i.e., the number of hours the patients remained in bed). Hence, both NIH-7519 and NIH-7525 resembled morphine in their pattern of effects.

TABLE 4

Average effects of drugs as compared with a placebo on certain physiological measurements for all subjects during the first 18 days of medication

Drug	Respiratory rate	Systolic blood pressure	Rectal temp., °C	Sleep, in hours	Activity hours	Inactivity hours
Placebo [a]	18.8	109.7	37.03	7.08	3.34	10.35
Morphine	13.8 [b]	109.2	37.07	6.86	2.65	11.20
NIH-7519	14.8 [b]	106.1	37.10	7.10	3.03	11.89
NIH-7525	14.0 [b]	109.7	37.04	6.74	2.57	11.10

[a] Each patient was on a placebo for 30 consecutive days, but this tabulation covers only the first 20 days on placebo.

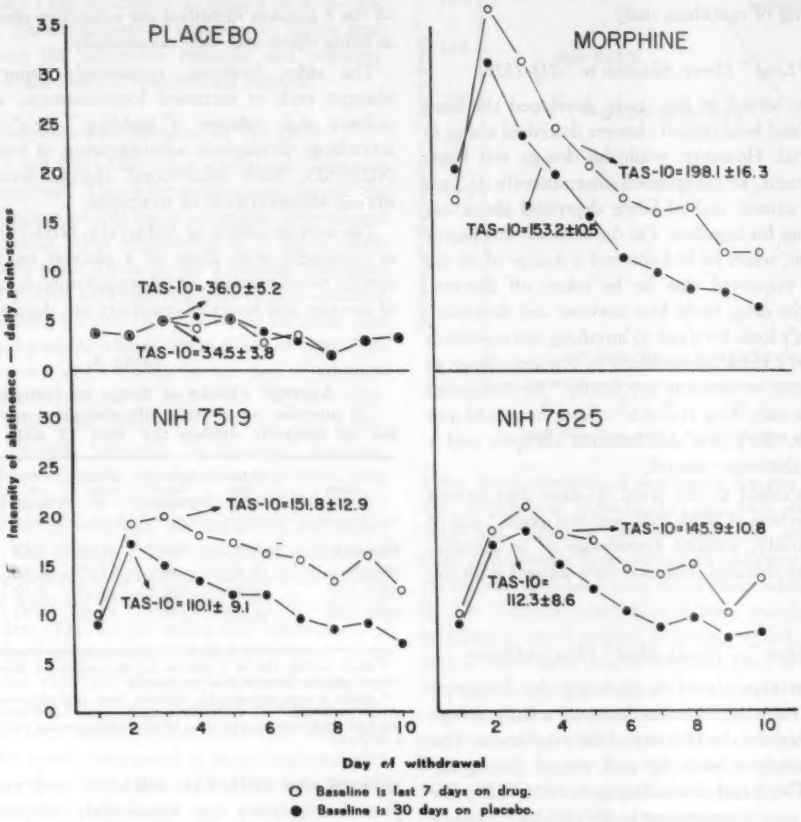
[b] Value is very significantly different from that observed when a placebo is given. The paired " t " value comparing morphine and a placebo is 11.18; comparing NIH-7519 and a placebo it is 11.86; and comparing NIH-7525 with a placebo it is 9.45.

Both patients and aides promptly reported the appearance of symptoms of abstinence when the drugs were discontinued.

Intensity of abstinence as indicated by daily point-scores and TAS-10 scores are shown for morphine, NIH-7519 and NIH-7525 (fig. 4). These are compared with the intensity of abstinence which was observed when a placebo was considered to be the drug of addiction. Intensity of abstinence following withdrawal of NIH-7519 and NIH-7525 was significantly less than that observed following withdrawal of morphine, as shown by the TAS-10 scores of these drugs compared with

FIGURE 4

Comparative intensity of abstinence after abrupt withdrawal of morphine, NIH-7519, NIH-7525 and placebo. As explained in the text, daily point-scores were computed both by using the averages for temperature, respiratory rate, etc., during the last seven days of addiction (standard Himmelsbach method), and also by using the averages during 30 days on placebo (modified Himmelsbach procedure). The TAS-10 values represent the mean areas (total intensity of abstinence for 10 days) plus or minus standard errors of the mean.



morphine (P is less than 0.02 when the areas were compared using both the standard and the modified Himmelsbach methods). The differences at the peak were also highly significant on the second day of abstinence (P was less than 0.01). On the third day of abstinence, however, the difference between morphine and NIH-7525 was not significant when the modified scoring method was used.

As compared with pre-drug values, chronic administration of medications did not provoke any significant alterations in white or red blood-cell counts, differential white-cell counts, hematocrit, sedimentation rates and urinalyses. There were no significant changes in body weight.

DISCUSSION

NIH-7519 has been found to be three to five times as potent as morphine as an analgesic in man (14, 10, 12), and NIH-7525 is approximately twice as potent as NIH-7519 (13). These values agree well with the figures on potency derived from pupillary constriction and euphorogenic qualities herein described.

Although Eckenhoff (4) and Prevoznik & Eckenhoff (12) have remarked on the paucity of side effects (including respiratory depression) with NIH-7519, respiratory depression during direct addiction experiments was just as great with NIH-7519 and NIH-7525 as it was with morphine.

One difference from morphine shared by both of these compounds is that the dosage of both, particularly NIH-7519, could not be increased proportionately as rapidly as that of morphine. When morphine was used in parallel addictive studies, it was always possible to increase the dosage from 40 mg daily to 180 to 345 mg daily (depending upon body weight) within the first 18 days of administration. In fact, it was possible to increase the dosage of morphine sulfate in non-tolerant former opiate addicts to 500 mg daily within ten days without the development of dangerous toxicity (6).

The data show unequivocally that NIH-7519 and NIH-7525 are addictive materials in man. Both drugs are potent euphoriants, both are far more potent than morphine in suppressing symptoms of abstinence from that drug, and both are completely adequate substitutes for morphine. Both drugs created physical dependence resembling that caused by morphine in direct addiction experiments, and definite abstinence occurred after withdrawal of both drugs after substitution for morphine for ten days.

Physical dependence on both drugs may be milder than on morphine, or may develop more slowly. The TAS-7 and TAS-10 scores were consistently lower than those predicted for equivalent doses of morphine after short direct addiction experiments and after substitution for morphine. The severity of abstinence in the one patient who received NIH-7519 for 127 days shows that under conditions of abuse, abstinence from this drug can, in some persons at least, be as severe as abstinence from morphine.

The great discrepancy in the potencies of both NIH-7519 and NIH-7525 in suppressing abstinence from morphine in man as compared with their potencies in suppressing abstinence in monkeys (3) is of course evident. For example, in man, 1 mg of NIH-7519 equals 8.15 mg of morphine, but in the monkey, 1 mg of NIH-7519 equals 0.18 mg of morphine — a disparity of 45-fold in the two species.[6] The opposite type of quantitative discrepancy in the two species is also known to occur, since the monkey is relatively sensitive to members of the meperidine group, whereas man is relatively insensitive. These species differences are chiefly quantitative and not qualitative, since most drugs so far tested which suppress abstinence in man will also suppress it in the monkey, even though the dosages in the two species may vary greatly.

[6] Dr. G. A. Deneau, of the Department of Pharmacology, University of Michigan, confirmed the chemical identity of the preparations used to estimate potency in monkeys and man.

Summary

1. The human pharmacology including addictiveness of *dl*-2′-Hydroxy-5,9-dimethyl-2(2-phenethyl)-6,7-benzmorphan HBr (NIH-7519) and *l*-3-Hydroxy-N-phenacylmorphinan methane sulfonate (NIH-7525) have been evaluated.

2. In single doses given by both the intravenous and subcutaneous routes, NIH-7519 and NIH-7525 are more potent than morphine in inducing subjective effects (euphoria), in provoking morphine-like behaviour, and in constricting the pupils.

3. Both NIH-7519 and NIH-7525 are potent suppressors of the morphine abstinence syndrome, and are completely adequate substitutes for morphine in addicted persons.

4. When the dosage of NIH-7519 and NIH-7525 was rapidly accelerated during chronic administration (addictive schedule), the over-all pattern, including side effects of both, was similar to that of morphine, except that it was not feasible to increase the dosage of NIH-7519 and NIH-7525 (especially the former) as rapidly as that of morphine.

5. Following withdrawal of NIH-7519 and NIH-7525, after substitution for morphine or after direct addiction, definite morphine-like abstinence phenomena appeared, which tended to be less severe than abstinence following withdrawal of equivalent amounts of morphine.

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Application of paper chromatography to the investigation of opium and opium alkaloids

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1. Introduction and Statement of the Problem

Paper chromatography in its many forms has proved to be a very valuable separation process. Experience has shown that both inorganic and organic ions and molecules of nearly all kinds of chemical substances can be separated even if the substances, as in homologous series, are very closely related chemically. The hydrocarbons are the only exception whose complete insolubility in water precludes separation by paper chromatography. If the sufficiently sharp separation of the substances is achieved, paper chromatograms can be used for isolating known and unknown substances; identifying pure substances and mixtures; purity tests of single substances and mixtures; checking of isolation and determination procedures; quantitative determination of numerous substances; and testing stability of medicinal preparations by the detection and quantitative determination of decomposition products. These general applications show that paper chromatography must be of the greatest value in the investigation of opium alkaloids and opium. Isolation of many of the side alkaloids in opium, which have been described but still insufficiently studied, can be successfully achieved by paper chromatography; moreover, paper chromatography has in fact shown that there must be further alkaloids present in opium which have not yet been described. In testing medicinal preparations this procedure has already been frequently used for identifying types of opium of different origins (1, 2), since it is considered possible to determine the country of origin of a sample by establishing the presence of specific side alkaloids, colouring matter and other impurities which are not found in other types of opium. It is also possible to determine the main and side alkaloids and impurities present in a preparation (e.g., opium pulvis, tinctura opii, extractum opii, opium cencentratum, opialum pulvis, ipecacuanhae opiatus or pulvis ipecacuanhae opiatus solubilis, etc.), so that these and other preparations containing opium alkaloids can be identified with certainty (3). Another obvious problem for research was the use of paper chromatography in purity tests of officinal opium alkaloids and salts, which the authors investigated (4) with good results. The sensitivity of paper chromatography in detecting opium alkaloids makes it possible to find an impurity of 1% of another alkaloid. This means of detecting small quantities of alkaloids can be used to check determinations of total or individual alkaloids in a drug or preparation. For the determination of morphine in opium, as laid down in *Ph. Helv. V*, we found in preliminary experiments (5) that with this procedure neither a quantitative extraction of morphine from opium, nor the separation of pure morphine is successful; this led us to carry out the experiments described in this paper. The results obtained showed us that all methods of quantitative determination of alkaloid drugs ought to be tested in this way. A quantitative paper chromatographic method for determining morphine in opium is described by Svendsen (6). Paper chromatography is also very useful for testing methods for the preparation of galenicals, because this method makes it possible to observe the progress of extraction of medicinal drugs and the behaviour of the active substances when making up tinctures, fluid extracts, dry extracts and so on. Paper chromatography could be used with advantage in a modern treatment of these problems. It is also very suitable for testing the stability of preparations. It would, for example, be extremely useful if the stability of opium alkaloids could be investigated during the opium extraction stage and storage. On this latter problem a valuable contribution has been made by Panopoulos & Vassiliou (1), who showed that 26 samples of opium from six different countries underwent no change in a year and a half; the chromatograms at the beginning and at the end of the storage period were identical. Similar research should be done on the galenical preparations of opium.

During the last few years we have done experimental work on a few of these multifarious problems. As a basis for further investigations on opium we first studied the separation of opium alkaloids and established the sensitivity of their detection. We then used these data for testing the purity of alkaloid salts and for checking the quantitative determination of morphine and of the most important side alkaloids in various types of opium.

2. The Paper Chromatographic Separation of the Most Important Opium Alkaloids

2.1 *Review of the Published Investigations*

The opium alkaloids have been the subject of repeated paper chromatographic investigations. Macheboeuf & Munier (7) described the separation of morphine, codeine and thebaine by means of a mixture of n-butanol + glacial acetic acid + water (100 + 100 + 50). The alkaloids applied as bases were well separated; but the authors found that under these conditions narcotine and papaverine could not be separated. Codeine and cryptopine behaved similarly. Butanol + glacial acetic acid + water (100 + 30 + saturation) also gave good separation of morphine, codeine and thebaine. By using buffered papers and propanol + water (3 + 1) the authors succeeded in separating thebaine (Rf = 0.75-0.78) from narcotine and papaverine (Rf = 0.94-0.96). Finally they separated morphine, codeine, thebaine, narcotine

or papaverine by soaking the paper in a salt solution (M/2 potassium chloride) which contains the same anion as the mobile phase. Using mobile phases capable of unlimited mixing with water such as acetone + water (3 + 1) they secured a separation of morphine, atropine and scopolamine. At the same time they established that the water content of such mobile phases is of significance for the spot form and that over 20% of water is required. A simultaneous separation of morphine and codeine with papaverine and narcotine was not achieved, however, by any of the methods tried. Svendsen (6) reported the quantitative determination of morphine from opium and the separation of morphine from other alkaloids. As a mobile phase he used acetic ether + formic acid + water (10 + 1 + 3). The author investigated, with n-butanol + glacial acetic acid + water (20 + 2 + 10), galenical preparations containing opium and tetrapon solutions. He characterized the partly separated alkaloids by means of colour reagents. He was not, however, successful in separating narcotine and papaverine. Mesnard & Boussmart (8) tested, with butanol + glacial acetic acid + water (50 + 15 + 15), injections containing, beside morphine, scopolamine, sparteine and strychnine. They were able to identify all of these alkaloids by paper chromatography. Vitte & Boussmart (9) examined a syrup, said to contain codeine ane dionine, because the common methods of detection were insufficient. They demonstrated by means of the size of the codeine spot that it was present in a quantity corresponding to that of codeine and dionine. Jatzkevitz (10), Salvesen & Paulsen (11), Wagner (12), Romano (13), Caronna & Bruno (14), Kaiser & Jori (15) separated opium alkaloids, partly synthetic morphine derivatives, spasmolytic and other alkaloids, without obtaining a simultaneous separation of papaverine and narcotine. Gore & Adshead (16) tested pure alkaloids, and/or their bases and salts by means of n-butanol + formic acid + water (10 + 1 + 10), n-butanol + acetic acid + water (40 + 10 + 50), and n-butanol + propionic acid + water (10 + 1 + 10) as mobile phases, and established that alkaloid bases and salts show an identical migration. Borke & Kirch (17), describe a method for painting glass plates with fluorescent substances. These plates are developed with dioxane. The disappearance of fluorescence shows the position of the alkaloids. The following Rf-values were found: narceine 0.0, morphine 0.38, codeine 0.62, papaverine 0.88, narcotine 0.92. Schute (18) separated morphine from the other opium alkaloids with 5% ammonia water as mobile phase. Reichelt (19) examined the paper chromatographic behaviour of 12 natural and partly synthetic opium alkaloids by means of formamide as stationary phase, and chloroform, benzene or a mixture of these solvents as mobile phase. With chloroform + benzene (2 + 3) the alkaloids are well separated, but not narcotine and papaverine. Vidic (20) investigated the opium alkaloids and spasmolytics from a forensic point of view. He studied the effect of the acid and of water in the system n-butanol + formic acid + water (12 + 1 + 7). He found a drop in the Rf-values during the first few days, and believes that this behaviour can be explained by the degree of saturation of the vapour space in the chromatographic chamber. For the chromatographic separation of opium alkaloids Asahina & Ono (21) used n-butanol + ammonia + water (50 + 9 + 15) as mobile phase and found the following Rf-values: narceine 0.58, morphine 0.72, codeine 0.93, narcotine 0.95, and papaverine 0.94. Schultz & Strauss (22) attempted to use paper chromatography for an analysis procedure. They investigated numerous alkaloids of the DAB 6 and its supplement (including morphine, codeine, papaverine and narcotine) by means of n-butanol + acetic acid + water (100 + 10 + 40), (100 + 20 + 53.5), (100 + 30 + 93.5); n-butanol + formic acid + water (120 + 10 + 70), and n-butanol + 0.1 N hydrochloric acid (50 + 50) as mobile phases. The separation of narcotine and papaverine, however, was achieved with none of the systems proposed. These authors indicate also the calculation of an Rf-value, used for the demixing mobile phase (n-butanol + hydrochloric acid). Mannering (23) deals with the paper chromatographic detection of opium alkaloids in urine and animal tissues. Isoamyl alcohol + concentrated ammonia + water (10 + 1 + 5) gives no better separation than the much employed n-butanol + acetic acid + water mixture. Tuderman & Krogerus (24) separated various alkaloid salts including morphine hydrochloride, codeine phosphate and papaverine hydrochloride. As mobile phases they used n-amyl alcohol + formic acid + water (100 + 18 + 4) on papers buffered with M/7 potassium phosphate, and as second mobile phase: isopropyl alcohol + water (75 + 25). They found the following Rf-values: morphine hydrochloride 0.16, codeine phosphate 0.33, and papaverine hydrochloride 0.94. Krogerus, Rautiainen & Westerlund (25) separated, by means of dioxane + formic acid + water (90 + 0.5 + 9.5), narcotine (Rf 0.89) and papaverine (Rf 0.77), but not codeine (Rf 0.21) and morphine (Rf 0.17). If acetic ether is used as second mobile phase in the same direction, morphine (Rf 0.52) and codeine (Rf 0.63) are separated afterwards. With acetic ether as mobile phase they also separated papaverine (Rf 0.53) and narcotine (Rf 0.85). Curry & Powell (26) tested alkaloid fractions in toxicological analyses and, with the system n-butanol + water + citric acid (5 + 5 + 1) on paper buffered with primary sodium citrate, found the following Rf-values: morphine 0.12, codeine 0.16, narcotine 0.47 and papaverine 0.48. Thies & Reuther (27) prevent the formation of ester in the solvent mixture butanol + glacial acetic acid + water by the addition of the corresponding ester. This reduces the Rf-values and improves the separability of the alkaloids considerably. With the mobile phase butyl acetate + n-butanol + glacial acetic acid + water (85 + 15 + 30 + saturation) they separated papaverine (Rf 0.57) from narcotine (Rf 0.70). Pfeifer (28) gives a method for the separation of the most important poppy alkaloids. First of all on buffered paper, pH 5.5 (citrate buffer) morphine (Rf 0.16), codeine (Rf 0.23), thebaine (Rf 0.61) and narceine (Rf 0.61) are separated from one another and from narcotine (Rf 0.91) and papaverine (Rf 0.92). The latter are finally separated with ammoniacal ether according to the Matthias method (29). Häussermann (30), with an aqueous solution of an electrolyte (250 g of ammonium sulphate, 250 ml of 2 N hydrochloric acid and water to 1,000 ml), separates narcotine and papaverine, but

not morphine and codeine with the following Rf-values: narcotine 0.43 to 0.45, papaverine 0.26 to 0.29, morphine 0.68, codeine 0.67 to 0.69, thebaine 0.47, and narceine about 0.4. The experiments carried out by Bettschart (31) for the paper chromatographic separation of opium alkaloids were basic to our investigations. Using water-saturated ether on a paper treated with an M/2 citric acid-phosphate buffer of pH 3.8, he separated narcotine (Rf 0.63) and papaverine (Rf 0.18). But he was not successful with this method in separating the other alkaloids. With a buffer of pH 7.4 he separated, by means of water-saturated ethylacetate, narceine (Rf 0.0), morphine (Rf 0.05), codeine (Rf 0.26), thebaine (Rf 0.82), laudanine (Rf 0.76), laudanosine (Rf 0.83) and cryptopine (Rf 0.67). With water-saturated n-butanol he obtained, on a similarly buffered paper of pH 6.8 the following Rf-values: morphine 0.38, codeine 0.56, narceine 0.74, laudanine 0.81, cryptopine 0.81, thebaine 0.84, narcotine and papaverine 0.96. Experiments with other mobile phases, such as benzene, mixtures of butanol and ether or chloroform, gave less successful separations. Graf & List (32), Mariani (33) and Burma (34) have recently separated narcotine and papaverine by paper electrophoresis. Hörhammer & Leue (35) tested tinctura opii simplex DAB6 with n-butanol + acetic acid + water (4 + 1 + 5). Under ultraviolet light they could identify five zones:

	Rf-value
Blue	0.86
Blue	0.74
	0.71
Light blue	0.57
	0.15

Macek, Hacaperkova & Kakac (36) examined, in a series of paper chromatographic analyses, the behaviour of about sixty natural alkaloids, including morphine, apomorphine, codeine, oxycodeinone, dihydroxycodeinone, heroin, ethylmorphine, narcotine, cotarnine, thebaine, narceine, cryptopine and papaverine. They separated the alkaloids using the following mobile phases: chloroform on paper impregnated with formamide + 1% acetic acid, benzene (chloroform) (1 + 1), formamide + benzene (1 + 1), methanol + 5% ammonia + benzene (1 + 1 + 2), n-butanol + acetic acid + water (4 + 1 + 5). Thiess & Reuther (37) examined the behaviour of alkaloids with various mobile phases in chromatograms. The mobile phases used were butylacetate + n-butanol + glacial acetic acid + water (85 + 15 + 40 + saturation) and butylacetate + glacial acetic acid + water (100 + 60 + saturation). For their experiments they used morphine (0.26, 0.24), codeine (0.39, 0.35), laudanine (0.53, 0.50), papaverine (0.65, 0.56), laudanosine (0.60, 0.53), narcotine (0.74, 0.65) and twenty others. An important contribution towards the systematic analysis of alkaloids with the help of paper chromatography was given by Waldi (38). This author developed a simple process for the identification of alkaloids by soaking four chromatographic papers with a solution of formamide-acetone, drying them, and, after applying the standard alkaloids and the solutions to be tested on the starting line, developing them with four solvents differing in polarity, using the system formamide-cyclohexane-chloroform-diethylamine. The polarity is varied by altering the ratio chloroform: cyclohexane. The Rf-values found are converted into R_{fk} values (values corrected according to the standard) and hR_{fk} values (i.e., hundredfold R_{fk} value). Of the opium alkaloids he dealt with narceine, morphine, papaverine, codeine and narcotine. The advantage of this method is that for every alkaloid four values are obtained and it therefore offers means for sure identification. Genest & Farmilo (39) described the paper chromatographic isolation, identification and determination of opium alkaloids (morphine, codeine, thebaine and papaverine) in pharmaceutical preparations. The mixtures contained, besides the alkaloid, acetylsalicylic acid, caffein, nicotinic acid, and nicotinic amide or phenacetine. The accuracy of the densitometric determination was good.

As the preceding review shows, the problem of separating the most important opium alkaloids (morphine, codeine, thebaine, narceine, narcotine, papaverine and cryptopine) in one process and on the same chromatogram has remained unsolved.

2.2. *Investigations on the Separation of the Opium Alkaloids*

By exploiting the details given in published work, and relying on our experiments with other alkaloids, we investigated, in preliminary experiments carried out on tested, pure standard alkaloids, the possibilities of separation. For this we used the following method:

2.2.1. *Use of an organic solvent as mobile phase:*

Without salt impregnation of the paper,
With salt impregnation of the paper using neutral salts, and
With impregnation of the paper using buffers.

2.2.2. *Use of an aqueous solution as mobile phase:*

Without addition of a salt to the mobile phase,
Adding a neutral salt to the mobile phase, and
Adding buffers to the mobile phase.

From these preliminary experiments we developed the

Chromatographic procedure A:

1. *Paper.* — Whatman paper No. 1, cut in sheets of 10-20/48 cm, running direction at right angles to fibre direction; where necessary treated with buffer solutions according to Kolthoff (40).

2. *Mobile phase.* — Isobutanol (50 ml), toluene (50 ml) saturated with water. Commercial isobutanol is purified by boiling for two hours with zinc dust and strong alkalis, followed by distillation and redistillation. Toluene is shaken with 7% sulphuric acid for four hours, the sulphuric acid drawn off, the toluene washed with a solution of sodium hydroxide and rectified.

3. *Application of the alkaloids.* — The alkaloids can be used either as bases or as salts, since no difference could be established in the behaviour of the various forms. They are dissolved in chloroform or methanol or in a mixture of these solvents. For slightly soluble alkaloids diluted organic acids or pyridine have been shown to be suitable. Immediately after the preparation the alkaloid solutions are applied by

means of a micropipette (Schellbach glass, subdivided in 0.001 ml, calibrated for delivery) on the starting line in quantities of 10 to 100 µg to alkaloid. The starting line is 9 cm from the upper edge of the paper sheet. The solutions are put on a circle of 1 cm diameter. The distance between two such circles should be about 3 cm. Large quantities of alkaloids should be applied in form of a stripe.

4. *Chromatography.* — For the descending development we used the Dumas apparatus (41) and worked, protected from strong light, in a place free from draughts and as far as possible at constant temperature (19° C to 21° C). On the floor of the chromatographic chamber, which is covered with water to a depth of 1 to 2 cm, stands a wide, flat dish containing the mobile phase. The walls of the chamber are covered with wet filter paper reaching to the floor of the chamber and dipping into the water. The chamber, thus papered, is left for forty-eight hours to allow the saturation of the interior. The paper sheet, prepared as in paragraph 3, is hung in the saturated chamber and conditioned for fourteen hours. Now the mobile phase is poured into the trough so that a depth of 15 mm is reached. The mobile phase, which at once begins to spread in the paper, is allowed to progress for 30 cm (about four hours and a half). Next the damp paper sheet is taken out of the chamber, the line reached is marked and the paper dried at room temperature (15-20 minutes).

5. *Detection of the alkaloids on the paper.* — The dried chromatogram is first examined under ultra-violet light and the fluorescing alkaloid spots marked by accurate outlining. Next the chromatograms are sprayed with reagents suitable for ultra-violet or visual detection. If an ultra-violet inspection is not required, the half-dried chromatograms can be sprayed at once with the reagents. This procedure is to be recommended, because it gives colour spots with sharp edges on white paper.

6. *Determination of the Rf-value.* — The spots which have appeared are outlined with pencil on the dry chromatograms and measured. The distance from the starting line to the centre of the spot is measured.

Detection of opium alkaloids on the chromatograph paper is best carried out with Dragendorff reagent in the composition given by Munier & Macheboeuf (42)

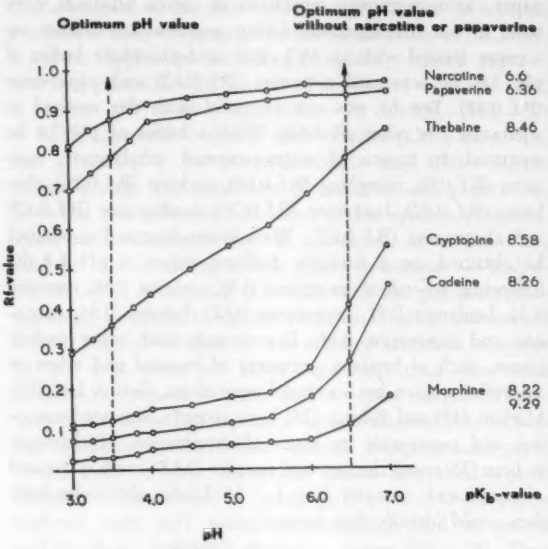
Solution A	
Bismuth subnitrate	850 mg
Water	40 ml
Glacial acetic acid	10 ml
Solution B	
Potassium iodide	8 g
Water	20 ml
Spraying solution	
Solution A	5 ml
Solution B	5 ml
Glacial acetic acid	20 ml
Water	100 ml

This reagent turned out to be the most sensitive; moreover, all the opium alkaloids investigated gave orange-red to rosy spots of great permanence.

FIGURE 1

Influence of the reaction of the stable phase on the separation of opium alkaloids

(Chromatographic procedure A)



2.2.3 *Influence of buffering of chromatographic papers on the separation of opium alkaloids*

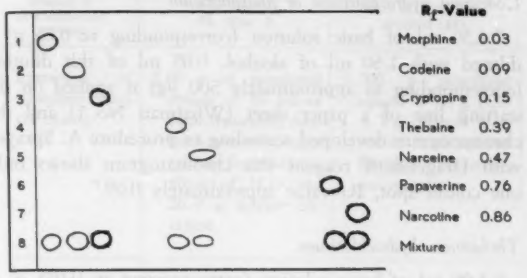
We used the succinic acid + borax and potassium dihydrogen phosphate + borax buffer solutions described by Kolthoff (40) because of their great stability (absence of carbon-dioxide-sensitive bases), their good buffer capacity, and their small salting-out effect. The chromatographic papers were thus buffered to various pH values between 3.0 and 7.0 and developed according to the chromatographic procedure A. The partition of the opium alkaloids examined is given in figure 1.

All the Rf-values increase as the pH rises. Narcotine and papaverine show a particularly great increase between pH 3.0 and 4.0. Thebaine rises regularly over the entire pH range examined. Morphine, codeine and cryptopine have sharply rising Rf-values towards neutrality. Narceine, which is omitted from this figure for the sake of clarity (pK_b-values 2.77 and 9.49) shows up to pH 5.8 an Rf-value above that of thebaine, which is rising regularly with it. At pH above 5.8 (buffer change) the Rf-value drops below that of thebaine (pH 7.0 = Rf-value 0.49). In comparing the Rf-values with the pK-values of the alkaloids investigated no parallelism could be discerned.

The optimum separation of the mixed opium alkaloids was obtained on papers buffered at pH 3.5. Here, morphine, codeine, cryptopine, thebaine, narceine, papaverine and narcotine are distinctly separated. If a solution of narcotine in chloroform is kept for 24 hours or over a longer period a spot is shown on the chromatogram which shines blue in ultra-violet light, is Dragendorff-negative, and has an Rf-value of 0.048. If narcotine or papaverine are not under

FIGURE 2

Separation of the mixed pure opium alkaloids at pH 3.5
(Chromatographic procedure A)

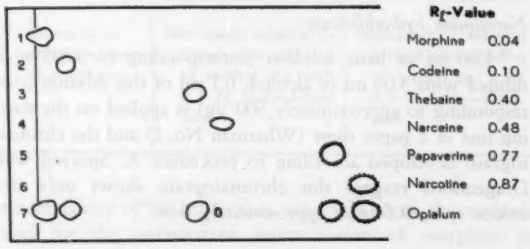


test, we suggest a separation at pH 6.6. The sequence of alkaloids will then be: morphine, codeine, cryptopine, narceine, thebaine, narcotine or papaverine.

Using chromatographic procedure A, pH 3.5, we were able to separate an Opialum *Ph. Helv. V* (morphine, codeine, thebaine, narcotine, papaverine and narceine as the hydrochlorides) prepared from our standard alkaloids. A solution containing 500 μg of Opialum was applied drop beside drop on the starting line. In this way we obtained broader but more compact spots, which were clearly visible (fig. 3).

FIGURE 3

Chromatogram of the individual alkaloids and of Opialum Ph. Helv. V *at pH 3.5*
(Chromatographic procedure A)



We checked the chromatographic procedure A at pH 3.5 on Extractum Opii, *Ph. Helv. V*. The separation of the alkaloids was excellent, but we could find no narceine in this preparation. This result was confirmed in the examination of the extract over the entire pH range from 3.0 to 7.0. Pantopon (Roche) gave the same result; narceine is also absent here. In both opium preparations no further alkaloids could be detected.

In table 1 all of the Rf-values are assembled as they were found in investigations on pure alkaloids, on opial and opium extract. They show adequate agreement, which is a further proof that constant Rf-values are obtained by using our method.

These results show that the most important opium alkaloids can be separated with sufficient precision. The Rf-values found differ by more than 0.05 Rf-units and all the alkaloid

TABLE 1

Rf-values of opium alkaloids

Alkaloid	Pure alkaloid	Opial	Opium extract
Morphine	0.03	0.04	0.029
Codeine	0.09	0.10	0.098
Cryptopine	0.15	—	0.15
Thebaine	0.39	0.40	0.39
Narceine	0.47	0.48	—
Papaverine	0.76	0.77	0.78
Narcotine	0.86	0.87	0.86

spots are compact and do not overlap. In the meantime our chromatographic procedure A has been tested by Farmilo, Genest, Clair, Nadeau, Sobolowski & Fiset (43) at pH 3.2.

These authors obtained approximately the same Rf-values: for all the alkaloids with the exception of narcotine they were very slightly higher, while that for narcotine was 0.03 units lower. Thus the separation of papaverine and narcotine was not so successfully achieved by them as by us. However, in numerous paper chromatographic analyses we have been able to verify our data.

3. The Sensitivity of Paper Chromatographic Detection of Opium Alkaloids

Once we had succeeded in separating the most important opium alkaloids, we determined the amounts of alkaloids which, with the current alkaloid reagents or under ultraviolet light, are just detectable on chromatographic paper. Accurately measured, increasing quantities of alkaloids were applied on papers buffered at pH 3.5, the chromatograms developed and the alkaloids revealed with the reagents listed in table 2. For a comparison with the limit values of detection in the literature, see table 2.

The sensitivity values we established were confirmed by Farmilo, Genest, Clair, Nadeau, Sobolowski & Fiset (46). Since, with the aid of the Dragendorff reagent at least 5 μg of alkaloid can be detected, and results obtained are always reliable, we used this reagent in every case for the detection of very small quantities of alkaloids.

4. Purity Tests of Opium Alkaloids by Paper Chromatography

Since preliminary experiments had shown that with the chromatographic procedure A, pH 3.5, very small quantities (5 μg) of alien alkaloid could be separated from relatively large quantities of alkaloid (up to 500 μg), the necessary requirements for a purity test of the opium alkaloids were fulfilled. For this purpose we applied 500 μg of the alkaloid base or salt on the prepared paper sheet, and developed the chromatograms according to procedure A (pH 3,5). The specifications for these purity tests can be formulated as follows:

Morphinum hydrochloricum

" 1.00 ml of basic solution (corresponding to 0.035 g) is diluted with 1.00 ml of alcohol. 0.06 ml of this dilution

TABLE 2

Sensitivity of the paper chromatographic detection of opium alkaloids

Alkaloid	Sensitivity in μg					
	Dragendorff-R	Mandel-R	Zaffaroni-R	Kiefer-R	Ultra-violet detection	Author
Morphine	5			1		44
	5	20			50	31
	60					24
	5			0.5		6
	5	20	10	1		*
Codeine	5	20				31
	30					24
	5	15	10		200	*
Thebaine	5	20			100	31
	5	15	10		100	*
Narcotine	5					30
	5	20			20	31
					20	45
	5	15	10		15	*
Narceine	5	20			> 50	31
	50 **	15			> 50	*
	20 ***					
Papaverine	5					30
	15					24
	5	20			0.5	31
					< 20	45
	5	15	10		3	*
Cryptopine	5	20				31
	5	20	5		50	*

Dragendorff reagent: Potassium iodobismuthate solution.
Mandel reagent: Solution of iodine in potassium iodide.
Zaffaroni reagent: Potassium iodoplatinate solution.
Kiefer reagent: Ferrichloride-potassium ferricyanide solution.

* Own experiments.
** pH below 5.8.
*** pH above 5.8.

(corresponding to approximately 525 μg) is applied on the starting line of a paper sheet (Whatman No. 1) and the chromatogram developed according to procedure A. Sprayed with Dragendorff or Kiefer reagent this chromatogram shows only one colour spot, Rf-value approximately 0.03."

Codeinum

" 0.125 g of codeine (accurately weighed) is dissolved in 5.00 ml of alcohol. 0.02 ml of this solution (corresponding to approximately 500 μg) is applied on the starting line of a paper sheet (Whatman No. 1) and the chromatogram developed according to procedure A. Sprayed with Dragendorff reagent this chromatogram shows only one colour spot, Rf-value approximately 0.09."

Codeinum hydrochloricum or phosphoricum

" 1.50 ml of basic solution (corresponding to 0.06 g) is diluted with 1.50 ml of alcohol. 0.05 ml of this dilution (corresponding to approximately 500 μg) is applied on the starting line of a paper sheet (Whatman No. 1) and the chromatogram developed according to procedure A. Sprayed with Dragendorff reagent this chromatogram shows only one colour spot, Rf-value approximately 0.09."

Thebainum hydrochloricum

" 1.00 ml of basic solution (corresponding to 0.035 g) is diluted with 1.00 ml of alcohol. 0.06 ml of this dilution (corresponding to approximately 525 μg) is applied on the starting line of a paper sheet (Whatman No. 1) and the chromatogram developed according to procedure A. Sprayed with Dragendorff reagent this chromatogram shows only one colour spot, Rf-value approximately 0.39."

Narceinum hydrochloricum

" 0.1 g of narceine hydrochloride (accurately weighed) is dissolved in 10.00 ml of methanol. 0.05 ml of this solution (corresponding to approximately 500 μg) is applied on the starting line of a paper sheet (Whatman No. 1) and the chromatogram developed according to procedure A. Sprayed with Dragendorff reagent this chromatogram shows only one colour spot, Rf-value approximately 0.47."

Narcotinum hydrochloricum

" 1.00 ml of basic solution (corresponding to 0.045 g) is diluted with 3.00 ml of alcohol. 0.1 ml of this dilution (corresponding to approximately 500 μg) is applied on the starting line of a paper sheet (Whatman No. 1) and the chromatogram developed according to procedure A. Sprayed with Dragendorff reagent this chromatogram shows only one colour spot, Rf-value approximately 0.86."

Papaverinum hydrochloricum

" 1.00 ml of basic solution (corresponding to 0.02 g) is diluted with 1.00 ml of alcohol. 0.1 ml of this dilution (corresponding to approximately 500 μg) is applied on the starting line of a paper sheet (Whatman No. 1) and the chromatogram developed according to procedure A. Sprayed with Dragendorff reagent or under ultra-violet light this chromatogram shows only one colour spot, Rf-value approximately 0.76."

5. Checking the Determination of Morphine in Opium by Paper Chromatography

5.1. *Arrangement of the Experiments*

After we had elaborated a method for the distinct separation of the most important opium alkaloids and established

TABLE 3

Investigated methods of morphine determination in opium

Phases of determination method	Lime method *Ph. Helv. V*	Eder & Wäckerlin method (48)	Mannich method (50)	Fischer & Folbert method (51)	Modified Büchi & Huber method
I. Extraction of morphine from the opium	5.00 g of powdered opium + 10 ml of H_2O triturated, then extracted with 2 g of calcium hydroxide + 40 g of H_2O and 26.0 g filtrate obtained	1,000 g powdered opium + 50 g H_2O + 2 g calcium hydroxide + manganese sulphate repeatedly macerated	1,000 g opium is extracted with 35 g H_2O with addition of lead acetate	1,000 g opium is triturated with 5 ml H_2O and the triturate is put on a column of 10 g aluminum oxide (Woelm, acid). Percolation of a total of 35 ml H_2O	1,000 g opium + 1 ml H_2O ground and mixed with 5 g aluminum oxide (Woelm, acid), put in chromatographic column containing aluminum oxide (Woelm, acid) and percolated with H_2O until 35 ml of filtrate are obtained
II. Separation of impurities	Addition of 2.5 ml alcohol + 12.5 ml ether + 1 g ammonium chloride	Lime extract shaken out with benzene-carbon tetrachloride 1 : 1 in order to remove subsidiary alkaloids. Lime extract buffered with ammonium sulphate			
III. Isolation of morphine	Morphine base precipitated and collected quantitatively on a Büchner glass funnel. Morphine dissolved in hot methyl alcohol in order to remove $CaCO_3$	Morphine shaken out with chloroform — isopropanol 3 : 1 and organic extract put through aluminum oxide (Brockmann); morphine precipitated with NH_4Cl, dissolved in methanol	Precipitation of morphine with chlordinitrobenzene in acetone and ammonia. After 12 hours the morphine ether is filtered off	Precipitation of morphine with chlordinitrobenzene	Precipitation with fluorodinitrobenzene
IV. Quantitative determination of morphine	Methanolic solution titrated after addition of methyl red with 0.1 N hydrochloric acid	Methanolic solution titrated after addition of methyl red with 0.1 N hydrochloric acid	Gravimetric determination after 1 hour's drying	Gravimetric determination	Gravimetric determination or determination in a non-aqueous medium.

the sensitivity of their detection, we could check the methods used for the quantitative determination of morphine in opium. The procedure we adopted was to use paper chromatography in examining the different phases in the methods for the determination of morphine:

Extraction of the opium powder (morphine content of the residue of extraction, composition of the opium extract)

Separation of the main quantity of impurities (composition of the morphine solution and of the mother liquor)

Isolation of the morphine (purity of the separated morphine with regard to a side alkaloid content)

Composition of the titrated base (presence of side alkaloids). We used the chromatographic procedure A.

The methods used for the determination of morphine in opium which we investigated are assembled, with an indication of the individual operations, in table 3.

For our investigation we used the following material:

(*a*) The *standard opium alkaloids* previously described

(*b*) The following *opium samples*

Opium I.....	Benares
Opium II	Turkey
Opium III	Iran
Opium IV	Yugoslavia

The opium samples I, III and IV originated as samples once sent by the League of Nations to various laboratories for elaborating a method of determination of morphine. They were packed in glass flasks sealed with paraffin-waxed corks and containing 30 g each. These samples were previously used by Eder & Wäckerlin (47, 48) and by Brunner (49) for their investigations. We were able to establish that, compared with earlier determinations (47), the moisture content had increased and the morphine content decreased in these samples.

5.2 *Check of the Various Methods*

5.2.1. *Lime method,* Ph. Helv. V

A common feature of the officinal lime methods is the extraction of the opium by a single maceration with lime water and the precipitation of the morphine directly out of the lime with ammonium chloride. An exception is made here by the USP XV, which extracts the opium with pure water. The lime methods aim, in a single treatment of the opium with calcium hydroxide and water, at getting a concentrated opium extract in order to keep the quantity of morphine remaining in the mother liquor as small as possible. Since a part of the liquid used for the extraction is retained by the opium pulp, it is not possible to obtain the entire extract for further treatment, and consequently the morphine can be determined only in an aliquot part of it.

The *Ph. Helv. V* and other pharmacopoeias allow for the increase in volume of the opium extract due to moisture and the extract substances of the opium by taking 26 ml of filtrate to be the equivalent of 25 ml of original liquor. Since moisture and the extracted matter vary from sample to sample of opium, this correction, as our experiments showed, is only approximate.

By checking the officinal lime method by paper chromatography (cf. fig. 4) we obtained the following results for the four opium samples:

A. *The lime extract (=A)* contains not only the morphine, but also considerable quantities of side alkaloids (chiefly codeine, with a little narceine, thebaine, papaverine and narcotine); hence this method of extraction leads to an inadequate separation of the side alkaloids.

B. *The ether phase (= B)* should dissolve only the side alkaloids, which get into the lime extract. But besides these a small quantity of morphine also gets into the ether and must be regarded as lost.

C. *The aqueous mother liquor (= C)* should contain no morphine, but considerable quantities of it remain in this phase and are lost to determination.

D. *From the titrated base (=D)* the major part of morphine was removed by ion exchange. It was, however, possible to detect considerable quantities of side alkaloids, particularly codeine, and traces of thebaine, papaverine and narcotine.

As a check on the complete extraction of the opium powder by this method, Schumacher (52a) carried out a second maceration with lime water and found by paper chromatography no morphine in this macerate; this points to a complete extraction.

Eder & Wäckerlin (47) examined the extraction procedure by single maceration of the opium with water and calcium hydroxide. They prepared for this purpose lime extracts of four different opium samples in the proportion 1 : 10, determined their morphine contents according to their shaking out method, and compared the results obtained with those they got by extraction of the opium in the proportion 1 : 50. The average morphine content in the concentrated extract was 10% lower. The authors therefore deny the possibility that a single treatment of the opium with the tenfold quantity of lime water will show the morphine quantitatively. It should, however, be observed that the morphine values obtained according to *Ph. Helv. V* are not far below those obtained by the Eder & Wäckerlin method (47). On the contrary, in the four opium samples examined they were almost all above them.

The explanation for this may lie in the fact that a less pure morphine is obtained for determination by the method of the *Ph. Helv. V*. Apart from the correctness of this argumentation, however, there must be a further reason for the difference between the morphine values found by Eder & Wäckerlin (47) with their method on the one hand and by the method of *Ph. Helv. V* on the other. These authors do not say how they prepared the extract 1 : 10. Probably they used the same method as for the diluted extract 1 : 50. In this case it may be that a larger quantity of morphine goes into the solution during the half-hour maceration specified by the *Ph. Helv. V* than in the extraction procedure of Eder & Wäckerlin (47) during which the solvent is in contact with the opium for much less time and a complete extraction is attained by repeated use of new quantities of solvent. The repetition and duration of maceration are decisive for this method.

In the case of the *Ph. Helv. V* specification the question of quantitative extraction is linked up with the question whether 26 ml of filtrate does in fact contain half of the morphine content of the opium. In the case of the *Brit. Ph. 1958* specification the question is the same with different figures. If the aliquot quantity of 26 ml of filtrate contains in fact half of the morphine present in the opium then the same quantity of morphine should be detectable in the residue and in the rest of the first filtrate. Proceeding from this consideration we extracted various opium samples according to the specification of *Ph. Helv. V*, took out 26 ml of filtrate and determined, in the manner given below, the quantity

TABLE 4

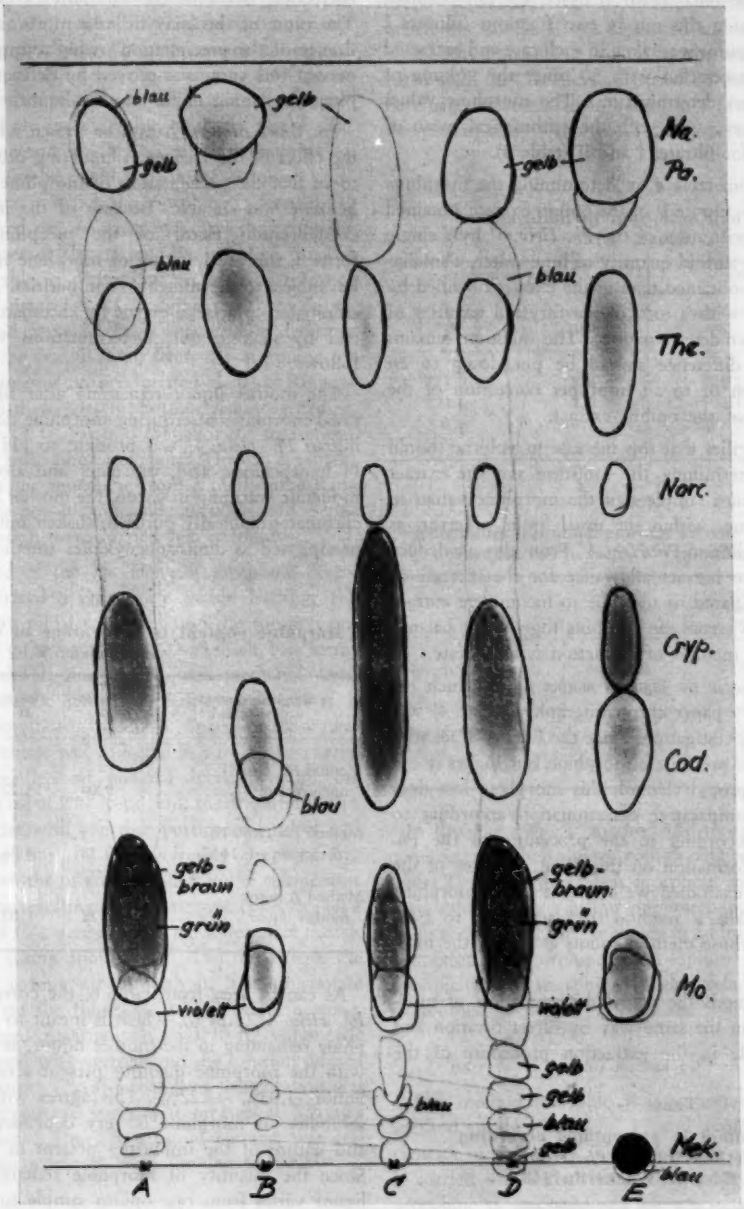
Morphine content in percentage by different extractions

	Opium I	Opium II	Opium III	Opium IV
Filtrate I				
(= aliquot part of	11.21	14.08	11.32	16.08
extract 1: 10, single	11.08	14.12	11.22	16.22
maceration)	11.26	14.20		16.15
Mean value	11.17	14.11	11.27	16.15
Filtrate II				
(= subsequent extraction	11.44	14.78	11.40	16.66
by repeated maceration	11.17	14.72	11.33	16.78
up to 1: 50)	11.59	14.60		16.54
Mean value	11.40	14.70	11.37	16.66
Direct determination				
(= repeated maceration	11.27	14.36	11.58	16.45
1: 50)	11.45	14.45	11.24	16.53
Mean value	11.36	14.40	11.41	16.49

FIGURE 4

Paper chromatographic check of the opium alkaloids in the different phases of the morphine determination by the lime method, Ph. Helv. V

(Chromatographic procedure A, pH 6.6)



Ph. Helv. V method

(Yugoslav opium, pH 6.6)

Blau	= blue	A	= Lime extract
Gelb	= yellow	B	= Ether phase
Braun	= brown	C	= Aqueous mother liquor
Grün	= green	D	= Titrated base
		E	= Standard opium alkaloids

of morphine present in it (= filtrate I). The opium residue was then further extracted, the second filtrate combined with the remainder of the first and again the quantity of morphine determined (filtrate II). As a comparison the same opium samples were once again analysed by this method, but instead of carrying this out in two fractions (filtrates I and II), 0.500 g of opium was taken in each case and extracted through repeated maceration with 50 times the volume of lime water (= direct determination). The morphine values so obtained agree very well with the arithmetical mean of morphine contents for filtrates I and II (table 4).

As can be seen from table 4, in determining the morphine in an aliquot part (= filtrate I) of the opium extract, obtained according to the specification of the *Ph. Helv. V* by a single maceration with the tenfold quantity of lime water, a smaller morphine content is obtained than in the extract obtained by repeated maceration with a total of the fiftyfold quantity of lime water (= direct determination). The question remains open whether this difference should be put down to an incomplete extraction or to an improper correction of the increase in volume of the opium extract.

The *Ph. Int. I* specifies that this increase in volume should be calculated by determining the moisture and the extract content for each opium sample, but the morphine values so obtained are the same, within the usual limits of error, as those obtained according to *Ph. Helv. V*. From this we deduce that the error due to inexact allowance for the increase in volume is small compared to that due to incomplete extraction. Since these two errors can combine together or balance each other out, this method of extraction is inaccurate.

The loss of morphine in the aqueous mother liquor which has been demonstrated by paper chromatography (figure 4) was subjected to further investigation. Since the Eder & Wäckerlin method (48) does not precipitate morphine but shakes it out with chloroform-isopropyl alcohol, this morphine loss does not occur, and a comparative determination according to their method and according to the procedure of the *Ph. Helv. V* can give information on this point. In three of the four opium samples examined we obtained lower morphine values by the *Ph. Helv. V* method than according to Eder & Wäckerlin (48), whose method counts as one of the most accurate (cf. table 5).

Since in both methods the actual determination of morphine is carried out in the same way by direct titration and since the error made in the extraction procedure of the *Ph. Helv. V* is not big enough to be regarded as responsible alone for the low pharmacopoeia values, the isolation of morphine must furthermore be defective in the way that a larger quantity of morphine remains in the mother liquor than the correction factor of the *Ph. Helv. V* will compensate for. The cause of this may lie in a more or less important hindrance of the precipitation owing to impurities. The correctness of this view was proved by determination of the morphine remaining in the mother liquor.

TABLE 5

Morphine content in percentage, according to the methods of the *Ph. Helv. V* and of Eder & Wäckerlin (48)

(Mean values of several determinations)

Method	Opium I	Opium II	Opium III	Opium IV
Ph. Helv. V	10.18	14.36	10.70	15.58
Eder & Wäckerlin.....	11.66	14.24	11.24	15.89

For this a method had to be chosen which would eliminate the effect of the substances hindering precipitation. It seemed to us that the precipitation of morphine with chlorodinitrobenzene was suitable. Because of the insolubility and high crystallization factor of the morphine-dinitrophenylether formed, the precipitation of morphine in this form is much less subject to the influence of impurities. These are, moreover, eliminated to a large extent by chromatographic purification and by shaking out. Determinations were carried out as follows:

The mother liquor remaining after filtering off the separated morphine base during morphine determination according to *Ph. Helv. V* was brought to pH 4-5 by addition of N hydrochloric acid, the ether and alcohol evaporated by moderate warming in vacuo, the mother liquor cooled down, chromatographically purified, shaken out, and the morphine precipitated as dinitrophenylether (method A).

TABLE 6

Morphine content in percentage of the lime extract, *Ph. Helv. V*

Morphine content according to:	Opium I	Opium II	Opium III	Opium IV
Method *Ph. Helv. V* uncorrected	9.04	13.22	9.56	14.44
Method *Ph. Helv. V* corrected (+1.14%)	10.18	14.36	10.70	15.58
Method A in the mother liquor	2.22	1.03	1.44	1.63

As can be seen from table 6, the correction factor of the *Ph. Helv. V* (1.14%), which is meant to allow for the morphine remaining in the mother liquor, is far from agreeing with the morphine quantity present actually in the mother liquor (1.03% - 2.22%). This agrees with the fact that the solubility of morphine is very dependent on the quantity and nature of the impurities present in the mother liquor. Since the quantity of morphine remaining in the mother liquor varies from one opium sample to another, it cannot be covered by a rigid correction factor.

For checking the purity of morphine subjected to determination, the chief method used hitherto was the determination of the methoxyl content (47, 53, 54), apart from ash analysis and determination of the optical rotation.

With the exception of oxydimorphine and protopine,

which, however, occur in opium only in very small quantities, all other side alkaloids of known constitution possess one or more methoxyl groups; morphine which contains side alkaloids also contains methoxyl. The methoxyl content of the morphine, however, gives no detailed information about the qualitative composition of the impurity and allows only rough estimates of the contents of side alkaloids. Thus, for example, one mg of methoxyl corresponds to 9.6 mg of codeine or 4.44 mg of narcotine (1 or 3 methoxyl groups). We carried out purity tests with the help of chromatographic methods. In the case of the *Ph. Helv. V* method we used as material that part of the filtered off morphine base which could be dissolved with methanol. This solution, in which the morphine is determined by titration, is coloured yellow to brown, and thus contains coloured impurities out of the opium. By paper chromatography (4) we were able to detect in it, in addition to morphine, considerable quantities of codeine, and traces of narcotine, thebaine and narceine. For a quantitative determination, we separated the side alkaloids from the morphine by ion exchange chromatography, precipitated them as Reineckates and determined them spectrophotometrically according to Lee Kum-Tatt & C. G. Farmilo (55). For the separation, we used the strongly basic anion exchanger, Dowex 2, which, in the base form, retains morphine from a methanolic solution in contrast to the non-phenolic side alkaloids (56). Separation and determination were carried out as follows:

The titration liquid of the *Ph. Helv. V* morphine determination was evaporated in vacuo by gentle heating, the residue dissolved in 10 ml of methanol, and this solution put on a column with 10 g Dowex 2 (X-4, 20-50 mesh, base form) in methanol. The column was washed with methanol, until no more codeine could be detected in 5 drops of eluate with 1% sodium tetraphenylboron solution. Speed of flow was 3-5 ml/minute. The eluate was collected in a round-bottomed flask, the solvent distilled off under reduced pressure, the residue dissolved in 5 ml of 2 N acetic acid, and transferred to a small beaker by rinsing with a further portion of 5 ml of 2 N acetic acid. After adding 10 ml of freshly prepared 2% Reinecke salt solution, the mixture was left in the refrigerator for half an hour. The resulting precipitate was collected on a Büchner glass funnel G4, washed with ice water until the filtrate was colourless (using about 20 ml) and freed from the adhering water by passing air through it. The precipitate was then dissolved on the funnel in 2 to 3 ml of acetone, the solution transferred quantitatively to a 10 ml volumetric flask, the funnel rinsed with acetone and the solution diluted with acetone to volume. The absorbance of this solution was measured in an appropriate spectrophotometer at 525 mμ using acetone as blank. The side alkaloid content was calculated as codeine according to the following formula:

$$X = \frac{D \times V \times M}{\varepsilon}$$

where X = the amount of alkaloid base found in mg
D = the optical density measured
V = the volume of the solution in ml
M = the molecular weight of the alkaloid base
E = the molar absorptivity of the alkaloid Reineckate (for codeine and morphine Reineckate: ε = 106.5)

In order to check the reliability of the described procedure, several separations of morphine-codeine mixtures were carried out. Codeine was separated and determined as indicated above. Morphine, bound by the anion exchanger, was eluted with 50% acetic acid (speed of flow, 3-5 ml/minute), the eluate concentrated in vacuo to a few ml and morphine precipitated with 1-chloro-2,4-dinitrobenzene (cf. table 7).

TABLE 7

Separation of morphine and codeine with Dowex 2

Quantities added		Quantities found	
Morphine mg	Codeine mg	Morphine mg	Codeine mg
127.3	5.8	124.2	5.7
194.0	7.3	190.4	7.4
300.8	18.2	297.3	18.0

TABLE 8

Subsidiary alkaloid content in the titration liquid according to *Ph. Helv. V* (calculated as codeine)

	Standard morphine mg	Codeine found mg	Codeine found %
Opium III	239.4	16.0	6.7
	236.6	15.5	6.5
Opium IV	360.5	18.4	5.1
	363.4	18.8	5.1

In the *Ph. Helv. V* method the morphine to be titrated contains, as table 8 shows, considerable amounts of side alkaloids. These are titrated as morphine and simulate therefore high values. This is in our opinion a source of serious errors in all the officinal lime methods in addition to the incomplete extraction of morphine from opium and the incomplete precipitation of morphine varying from one opium sample to another.

5.2.2. *Eder & Wäckerlin method* (48)

This method (cf. table 3) is an improvement of the lime method of the *Ph. Helv. V*, and avoids some of the deficiencies of the latter. The extraction of the opium powder is carried out with a fiftyfold quantity of lime water, and morphine is separated not by precipitation but by shaking out with chloroform-isopropyl alcohol.

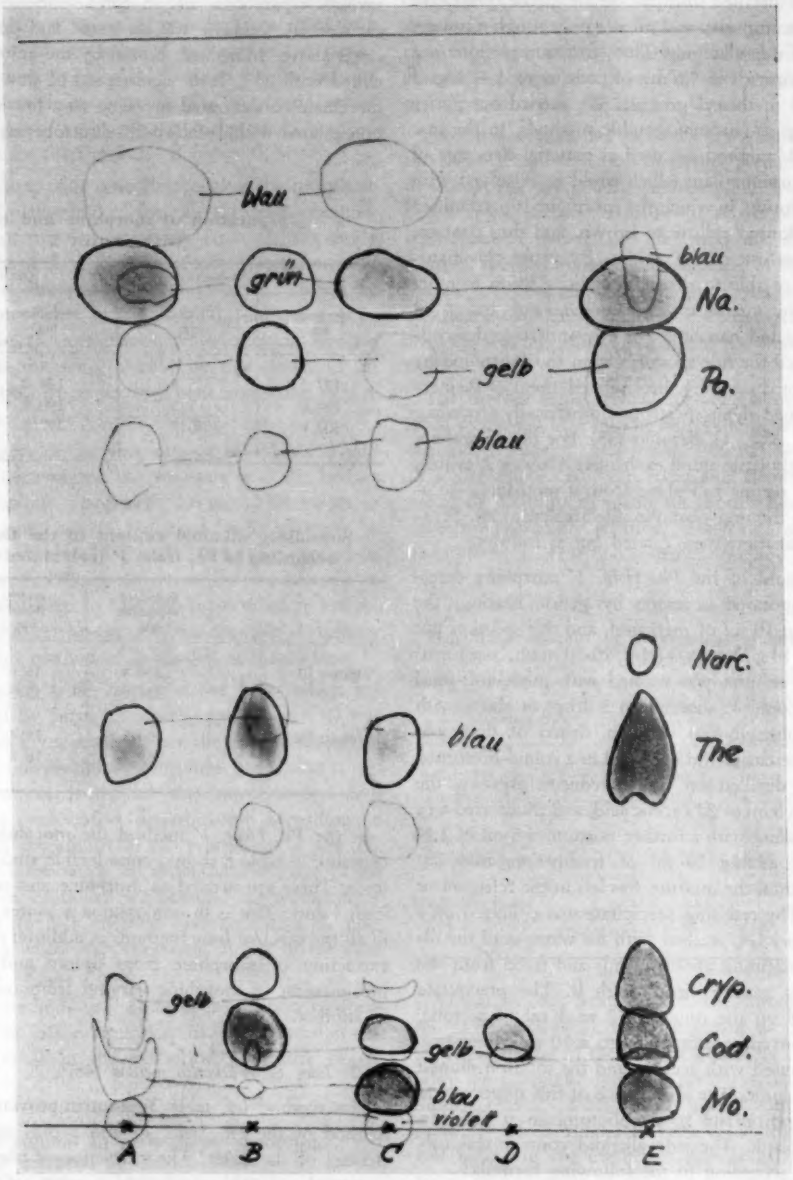
In checking this method by paper chromatography we obtained the following results (figure 5):

A. The extracted *opium residue* was re-extracted with 30 ml of N hydrochloric acid, and this extract (= A) chromatographed. It contained neither morphine nor codeine, but

FIGURE 5

Paper chromatographic test of opium alkaloids in the various phases of morphine determination according to Eder & Wäckerlin (48)

(Chromatographic procedure A, pH 3.0)



Eder & Wäckerlin method 1940
(Yugoslavia opium pH 3.0)

Blau = blue
Gelb = yellow
Grün = green

A = Second opium extract
B = Benzene-carbon tetrachloride extract
C = Aqueous mother liquor of the morphine precipitate
D = Titrated base
E = Standard opium alkaloids

thebaine and papaverine and small quantities of narcotine were present.

B. The *benzene-carbon tetrachloride extract of the side alkaloids* (= B) contained codeine, cryptopine, thebaine, narcotine, and porphyroxine-meconidine, but no morphine.

C. *The aqueous mother liquor of the morphine precipitate* (= C) contains in addition to side alkaloids a fairly large quantity of morphine, which is lost.

D. From *the titrated base* (= D) the major part of morphine was removed by ion exchange. In the remaining solution codeine could be detected.

The quantity of morphine remaining in the mother liquor after precipitation has been commonly compensated for by a correction factor obtained in experiments with pure morphine base. But the use of this factor for the determination of morphine in opium is only justified if the purification of the morphine isolated from opium is so complete that it is as pure as the morphine used in establishing the correction factor. That this condition is not fulfilled, and that the correction factor obtained with pure morphine for the determination in opium is too small, results from the fact that the addition of another purifying operation (filtration of the morphine extract with aluminum oxide) in the 1937 method raised the values for morphine by up to 0.5 per cent, although the correction for the losses in the mother liquor remained the same. Our experiments have shown that after the evaporation of the solvent the morphine extract still contains 10%-20% of impurities, and it is therefore to be expected that precipitation will be partly hindered. We determined the quantity of morphine actually retained in the mother liquor in the following way.

The mother liquor obtained by filtering off the precipitated morphine base was transferred directly in a separating funnel and shaken out several times with chloroform isopropyl alcohol 3 : 1. The combined extracts (about 70 ml) were collected in a flask, the solvent distilled off and the residue dissolved in 10 ml of methanol. The separation of the morphine from the side alkaloids was carried out by ion exchange as described (p. 35). The morphine eluted from the column was precipitated as Reineckate and determined spectrophotometrically as described for codeine on page 35.

The results of this determination are given in table 9. While, with a pure morphine base 4.4 mg of morphine remained dissolved in the mother liquor, we found in the mother liquors of morphine determinations in opium (10.4 - 17.9 mg of morphine) much larger quantities, varying from sample to sample of opium. This result shows once again that the losses in the mother liquor cannot be accounted for by a rigid correction factor. In a further series of experiments we precipitated the morphine not as base but as dinitrophenylether. In this way we found it possible to secure the entire quantity of morphine and to avoid the uncertain factor for losses in the mother liquor. For the detection of any alkaloidal impurities in the morphine subjected to titration, the titrated solution was evaporated in vacuo, the residue dissolved in methanol, and the side alkaloids separated by ion exchange from morphine. By paper chromatography (4) we could detect only codeine as an impurity and thus calculate its amount with the aid of the methoxyl content established by Eder & Wäckerlin (48). Compared with the officinal lime methods the codeine content of the morphine to be titrated is relatively low (16% - 29%). This underlines the necessity to remove the side alkaloids as completely as possible before the precipitation of morphine as a base.

TABLE 9

Checking of the Eder & Wäckerlin method (48)

	Opium I	Opium II	Opium III	Opium IV
Extract content in %	61.30	60.59	63.87	62.13
pH of mother liquor	8.77	8.71	8.68	8.76
Raw morphine in g	0.1260	0.1661	0.1353	0.1870
Morphine content in %	11.72 11.60	14.18 14.30	11.29 11.18	15.95 15.84
Methoxyl content in mg ... calculated as codeine in mg.	0.24 2.3		0.17 1.6	0.30 2.9
Mg of morphine in the mother liquor	12.4	10.3	12.8	17.9
Morphine content in % after precipitation as dinitrophenylether	11.40	14.36	11.38	16.32

The quantitative precipitation of the pure morphine base offers in all methods so far mentioned the greatest difficulty and is, as our investigations have shown, even in the otherwise well worked out Eder & Wäckerlin (48) method, not complete. Moreover, this operation increases considerably the time required for a morphine determination, since 12 to 24 hours must be allowed for precipitation.

It was therefore obvious that one must attempt, in working out new methods of morphine determination, to replace the precipitation of the morphine base as a means of purification by other purifying procedures which are quicker and more sure in effect. A method of morphine determination issued by the Secretariat of the United Nations (57) aims to isolate the morphine as pure as possible by a series of extractions, so that it can be titrated without recrystallization.

6,00 g of opium are extracted with the 15-fold quantity of lime water by a single maceration. An aliquot part of the extract is transferred to a separator and after addition of ammonium chloride extracted for 4 to 5 hours with ether-acetone 3 : 2. The organic extract carries all the alkaloids.

The solvent is distilled off, the residue dissolved in chloroform and this solution is shaken out with dilute dichloracetic acid, in which morphine is soluble. After addition of ammonia, this solution is shaken out with a mixture of chloroform and isobutyl alcohol (3 : 2) and the solvent distilled off. The residue is dissolved in methanol and morphine determined titrimetrically.

This method is deficient in certain points. The extraction of an unnecessarily large quantity of opium is performed by single maceration, by which, as has been shown for the official lime methods, not all of the morphine is extracted. The necessary correction for the increase in volume of the opium extract and the further treatment of an aliquot part of it are further sources of error. This method was subjected to a detailed criticism (58).

Knafft-Lenz (59) attempted, by a special method of extraction and by a series of extractions of the morphine, to isolate it from the opium in so pure a state that it could be directly determined by titration.

3.00 g of opium dried at 105° C are digested with carbon tetrachloride and the solvent filtered off. After addition of sodium sulphate the opium residue is digested several times with water. An aliquot part of the opium extract is shaken out with benzene to separate the side alkaloids, and after addition of sodium bicarbonate with a chloroform-ethanol mixture in order to obtain the morphine. The solvent is distilled off, the morphine remaining is dissolved in an excess of acid and determined by indirect titration.

The method offers no significant advantage in comparison to the extraction methods used hitherto, except that the usual precipitation of the morphine base as a means of purification is omitted or replaced by re-crystallization which can be carried out more quickly. The method of extraction described is very cumbrous, since the opium residue must be repeatedly transferred from the filter to a flask for re-extraction. The treatment of the opium with carbon tetrachloride removes fatty matter, a part of the side alkaloids, and even small quantities of morphine, as we were able to provide in our paper chromatographic tests. The author (54) obviously based the development of this method on the insolubility of pure morphine base and of its salts in carbon tetrachloride. This is not, however, the case for the morphine to be found in opium, since the impurities considerably enhance its solubility. The side alkaloids are not completely separated from the morphine by the single shaking out of the opium extract with benzene, so that the morphine to be titrated still contains side alkaloids. The morphine isolated from our opium samples and remaining after the evaporation of the solvent used in the extraction process showed a fairly strong brown colour and therefore contained in addition to side alkaloids some opium impurities. As can be seen by comparison of the values obtained according to various methods shown in table 20, the values obtained by the Knafft-Lenz (59) method show rather low morphine contents. In the following table 10 are given the values found in dried opium by this method and the values calculated for undried opium.

TABLE 10

Morphine content in percentage according to the Knafft-Lenz method (59)

	Dried opium	Undried opium
Opium I	11.34	10.70
	11.27	10.63
Opium III	11.01	10.47
	10.92	10.40

Graf (60) attempted by means of chromatography to isolate the morphine from the opium in such a pure state that it could be determined directly by titration.

0.200 g of opium is digested with 1 ml of water, the mixture alkalized, and ground with kieselguhr. The mass is put into a chromatographic tube and percolated first with dichlorethylene to remove the side alkaloids, and then with chloroform/isopropanol 3 : 1 in order to obtain morphine. The solvent of the morphine fraction is distilled off, the residue dissolved in methanol and the morphine titrated with 0.1 N hydrochloric acid, using methyl red as indicator, to a " strong red colour ".

We tested this procedure, which is very simple in principle and practice, first with a mixture of pure opium alkaloids, which we treated in the same way as is prescribed for opium. Graf (60) does not give a detailed definition of the kind of kieselguhr which he used, and only prescribes a type which is as little absorbent as possible. For our experiments we used " Hyflo Super-Cel " (Johns-Manville Co., London). The dichlorethylene used for the elution of the side alkaloids was collected in three fractions of 30 ml each, and each fraction separately examined by paper chromatography (4). Every one of the three fractions contained, in addition to the side alkaloids, some morphine, which in this way is lost to determination. The morphine fraction, on the other hand, was free of side alkaloids. With " Hyflo Super-Cel " as carrier and dichlorethylene as solvent, it is therefore possible to separate by chromatography the side alkaloids quantitatively from morphine, but some morphine is lost. Graf's indication (60) to titrate to a " strongly red colour " is imprecise, and is presumably intended to represent a kind of correction factor, which, however, can certainly not be used for every type of opium. In our experiments we titrated the morphine first to the end point of methyl red and then to a strongly red colour. The titration liquid was then evaporated in vacuo, the residue dissolved in 5 ml of 2 N acetic acid, the morphine precipitated as Reineckate and determined spectrophotometrically (cf. p. 35).

As can be seen from table 11, we did not succeed, with the prescribed procedure, to recover the quantity of morphine taken. Since we were able to show by paper chromatography, that morphine was eluted partly with the side alkaloids, the results correspond to our expectations. In opium, the solubility of morphine in dichlorethylene is further increased by the many impurities, so that even higher losses can occur.

TABLE 11

Test of the Graf method (60) with pure alkaloids

Quantity of morphine base taken mg		Quantity of morphine base found mg		
(*a*)	(*b*)	(*a*)	(*b*)	
28.85	25.4	25.6	23.1	Titrated to colour change
		27.0	24.5	Titrated to "strong red"
		25.1	23.1	Titrated as Reineckate

The residue remaining after the distillation of the solvent of opium extracts is coloured dark brown; it is therefore clear that with the morphine some coloured impurities are eluted from the opium, which, if they contain acid or basic groups, will interfere in the titration of morphine. We therefore precipitated the morphine after titration as Reineckate and determined it spectrophotometrically (cf. p. 35). The morphine values found according to this method lie partly below, and partly above, those found by titration (cf. table 12), which shows that one cannot deduce directly the true morphine content from the amount of acid to neutralize the morphine solution. We regard as further sources of error a possible oxydative decomposition of morphine by the addition of ammonia to the hot opium trituration, and the possibility that ammonia is eluted with the chloroform-isopropanol mixture and interferes thus in the titration. In table 12 are given the morphine values obtained according to the Graf method (60). A comparison with the values found by other methods is given in table 20.

5.2.3. *Mannich method* (50)

The method (see table 3) depends on the reaction of the morphine extracted from opium with 1-chloro-2.4-dinitrobenzene to a very insoluble morphine-dinitrophenylether. The extraction of morphine from opium can be done according to Mannich (50) in three different ways: by single maceration, by repeated maceration or by percolation. The first-named procedure was adopted by the Svenska Farmakopén. Even according to Mannich's own data (50), the extraction of morphine is not complete, since the increase in volume of the opium extract owing to moisture of opium, as well as the extracted substances, are accounted for only by a rigid correction factor. This procedure presents the same deficiencies as the officinal lime methods; incomplete extraction and a not always accurate measurement of the aliquot part of the opium extract. By repeated maceration or by percolation of the opium, on the other hand, all the morphine is extracted.

TABLE 12

Morphine content in percentage according to the Graf method (60)

	Titrated according to Graf	Precipitated as Reineckate
Opium I	11.12 11.10	11.2
Opium III	9.99 9.80	11.1
Opium IV	15.73 15.68	15.9

The checking of this method by paper chromatography gives the following results (figure 6):

A. The *opium residue*, extracted by repeated maceration or by percolation with the 35-fold quantity of water, was re-extracted with methanol and N hydrochloric acid (= A). In this second extract neither morphine nor codeine could be detected, but it did contain papaverine and narcotine. The extraction of morphine according to the Mannich method is therefore quantitative.

B. The *mother liquor of the morphine ether precipitate* (= B) contains no free morphine, from which it can be deduced that morphine is precipitated quantitatively as ether.

C. *The morphine-dinitrophenylether* (= C) was free from morphine. By digesting a large quantity of morphine-ether with methanol, codeine could be detected.

A considerable quantity of non alkaloidal impurities is precipitated by lead acetate, so that an opium extract obtained by addition of this salt is considerably paler than a pure water extract. Mannich (50) states that owing to lead acetate the acidity of the opium extracts is shifted from slightly acid to a nearly neutral point (from pH 3 to pH 6). We were unable to observe such a pH-shift in the opium samples which we examined. After the addition of the prescribed quantity of lead acetate there occurred only a negligible pH-shift towards neutrality; in one case (opium II), on the contrary, we observed a decrease of the pH. As can be seen from the data assembled in table 13, the pH values of the different opium extracts are very near one to another, due to lead acetate, but the weaker bases (narcotine and papaverine) are not precipitated. Accordingly we found, by paper chromatography, in the opium extracts obtained by the Mannich (50) method, considerable quantities of these alkaloids.

The precipitation of morphine by conversion to the very insoluble morphine-dinitrophenylether is quantitative, for we

TABLE 13

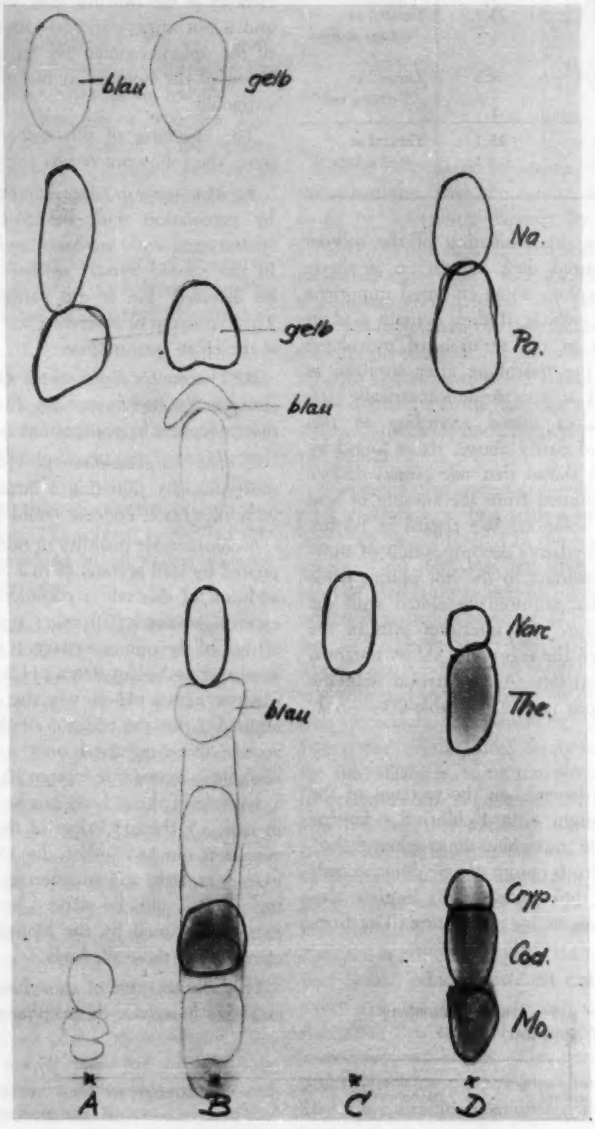
Influence of lead acetate on the pH-value of the opium extracts

pH-value	Opium I	Opium II	Opium III	Opium IV
Aqueous opium extract	4.02	5.45	3.78	4.14
After addition of lead acetate	4.65	4.86	4.58	4.73

FIGURE 6

Testing of opium alkaloids in various phases of the morphine determination according to Mannich (50) by paper chromatography

(Chromatographic procedure A, pH 3.0)



Blau = blue
Gelb = yellow

A = opium residue re-extracted
B = mother liquor of the morphine-ether precipitate
C = morphine-ether
D = pure alkaloids

were unable to detect by paper chromatography any free morphine in the mother liquor. The morphine-ether formed is, indeed, slightly soluble in the mother liquor. The losses are, however, slight (about 2 mg) and are compensated by the slight impurities in the precipitated morphine ether, so that a correction factor is not necessary. To establish the purity of the precipitated morphine-ether, several authors have chiefly determined the methoxyl content, which permits indeed rough estimates of the side alkaloids content (codeine), but gives no indication of the amount of methoxyl-free impurities. Morphine-dinitrophenylether as a weak base can be titrated with 0.1 N hydrochloric acid (50) or in a nonaqueous medium with perchloric acid (61), whereby not titratable impurities can be detected. We checked the purity of the precipitated morphine-dinitrophenylether on the one hand by paper chromatography and on the other by comparison of the titrimetric and gravimetric determination. By titrating with 0.1 N hydrochloric acid and methyl orange as indicator, the end point is only recognizable with difficulty. Methyl red gives a sharper end point, but it occurs too early, so that corrections have to be made (50, 54). We decided therefore on the titration with perchloric acid, where a very sharp end point is obtained with crystal violet as indicator. Only by digesting larger quantities of morphine-dinitrophenylether (about 1 g) with methanol and filtering off the ether, which in contrast to the free alkaloids is very slightly soluble in this solvent, we were able to detect by paper chromatography small amounts of codeine in the concentrated methanolic solution.

As can be seen from table 14, higher morphine values are obtained with the Mannich method than with the other methods mentioned so far, which can be ascribed to the fact that all the morphine present in the opium extract is dealt with. This fact demonstrates the advantage that, compared with the lime methods, no correction factor is necessary. From a comparison of the morphine values obtained by gravimetric and titrimetric determinations of the morphine-dinitrophenylether it can be seen that it is more or less impure according to the opium sample. Vollmer (62) pointed out that the nature and quantity of the colloid substances present in the mother liquor account for the fact that the morphine-dinitrophenylether precipitated is capable of carrying down small quantities of side alkaloids. The purification of the opium extract from which the morphine-dinitrophenylether is to be precipitated is, therefore, in this method, the most urgent problem. In order to avoid these sources of errors, van Pinxteren & Smeets (54) and Witte (63) precipitated the morphine from a lime extract purified with manganese chloride, and Böhme & Strohecker (64) purify the opium extract by chromatography on aluminum oxide. This accurate but rather troublesome and lengthy process was quite considerably simplified by Fischer & Folberth (51) (see table 3) so that this method seems to be suited for replacing the original method of Mannich (50). The aluminum oxide column retains a large quantity of the ballast substances, recognizable on the brown colouration of the aluminum oxide and the pale yellow colour of the extract. The extraction is, however, rather difficult, since the opium particles settling on the upper surface of the aluminum oxide form a compact mass, through which the water can pass only with difficulty. Thereby, the quantitative extraction of the morphine is prejudiced. It is to this that we ascribe the deviation of the morphine values found with one opium sample (±0.2%). Neither is the apparative arrangement required for the extraction very advantageous (" the Allihn filter tube containing aluminum oxide is placed on a Witt's filter apparatus which contains an Erlenmeyer flask to collect the filtrate "). Since, however, the method is in principle very simple and can be carried out with a minimum of time, apparatus and reagents, we decided to propose it in modified form as a new pharmacopoeial method.

TABLE 14

Morphine content in percentage according to the Mannich method and titrimetric determination with perchloric acid

	Single maceration (*Svenska Farmakopén*)		Repeated maceration	
	Gravimetric	Titrimetric	Gravimetric	Titrimetric
Opium I	11.56 11.57	11.21	11.91 11.83	11.52 11.47
Opium II	14.55 14.65	14.24	14.80 14.92	14.65 14.78
Opium III	11.27 11.18	11.15	11.54 11.40	11.41 11.34
Opium IV	15.72 15.85	15.68	16.18 16.23	15.98 16.02

Svendsen & Aarnes (65) also use aluminum oxide for the purification of the opium extract, but extract the opium, not with water, but with an organic solvent. The method was adopted by Garratt, Johnson & Lloyd (61) and modified in some points. They ground the opium powder, after addition of ammonia and ethanol, with aluminum oxide (standardized according to Brockmann) and eluted it in a chromatographic tube with chloroform/isopropanol 3 : 1. The morphine is shaken out of the organic phase with sodium hydroxide solution, precipitated with 1-fluoro-2.4-dinitrobenzene as proposed by Dann & Wippern (66), and determined gravimetrically.

In order to make sure whether 100 ml of the chloroform-isopropanol mixture (Svendsen & Aarnes (65) prescribe 240 ml) extract morphine quantitatively from opium, we extracted the opium residue two times with 50 ml of the solvent mixture. In contrast to the first extract these re-extracts were almost colourless, but the first 50 ml contained, as we were able to show by paper chromatography (4), small quantities of morphine, while the second re-extract in the four opium samples examined was free of morphine. In order to determine the morphine content in the first re-extract the solvent was distilled off, the residue dissolved in 30 ml of acetone, and 0.25 g of chloro-dinitrobenzene, 4 ml of 25% ammonia and

36 ml of water added. This solution was still perfectly clear after twelve hours and showed a slight turbidity only after seeding with morphine-dinitrophenylether.

Blanks with 1, 2 and 3 mg of morphine base showed that 2 mg of morphine give a slight turbidity after seeding, while the solution with 1 mg remained perfectly clear, and that with 3 mg showed a slight precipitation. The morphine quantity remaining in the opium residue could therefore have been no more than 2 mg (= 0.2% of the quantity of opium taken). As this finding was the same in all four opium samples, we regard the required quantity of solvent as insufficient to secure a quantitative extraction of morphine. After percolation with 150 ml of chloroform-isopropanol no morphine could be detected by paper chromatography in the residue. In the extracts, emulsions were sometimes formed, which separated often after a long time. The morphine values found by this method correspond to those given by Mannich (50). The greater purity of the precipitated morphine-dinitrophenylether follows from the close agreement between the gravimetric and titrimetric values found. These values are given in table 15.

TABLE 15

Morphine content in percentage according to the method of Garratt, Johnson & Lloyd (61)

	Opium I	Opium II	Opium III	Opium IV
Gravimetrically	11.70 11.64	14.70 14.59	11.25 11.30	16.28 16.37
Titrimetrically	11.59	14.50	11.22	16.20

5.2.4. *Establishment of a modified method of morphine determination for pharmacopoeial purposes*

The critical examination of the officinal lime methods showed the following considerable deficiencies:

an incomplete extraction of morphine from opium,

the loss of morphine to a degree which cannot be checked during its precipitation,

impurities in the morphine to be titrated consisting of 5 - 10% of side alkaloids,

the use of a comparatively large quantity of opium for the determination, and

too lengthy a process of determination.

Our experiments with the Mannich method (50) and its modifications led us to expect that the deficiencies described above could be best avoided by improving this procedure. We therefore revised the different phases of these processes, as described in the following.

Extraction of morphine from opium powder. — (1.000 g of opium powder is ground with 1 ml of water and 5 g of aluminum oxide (Woelm, acid), put on a column of a further 5 g of aluminum oxide (Woelm, acid) and percolated with water, until 35 ml of eluate is obtained. For technical improvements see specification, page 44).

The extraction of morphine from opium proceeds quantitatively in the method given. By paper chromatography we could detect in re-extractions of the column with water and N hydrochloric acid slight quantities of side alkaloids, chiefly narcotine, but no morphine. Filtration through aluminum oxide provides a satisfactory purification of the opium extract, as recognized on its much clearer colour compared with an untreated water extract and by the brown colouration of the aluminum oxide. In table 16 the extract contents of water extracts from various opium samples with and without filtration through aluminum oxide are compared.

TABLE 16

Extract contents in percentage of aqueous extracts with and without filtration through aluminum oxide (Woelm, acid)

(Opium powder = 100%)

Water extract 1 : 35	Opium I	Opium II	Opium III	Opium IV
Untreated	52.8	47.1	64.5	58.9
Filtered through aluminum oxide	48.1	35.6	49.2	42.0

Precipitation of morphine with 1-fluoro- or 1-chloro-2.4-dinitrobenzene. — (35 ml of opium extract + 4 ml of 25% ammonia + 0.25 g of 1-fluoro- (or 1-chloro-) 2.4-dinitrobenzene in 30 ml of acetone are shaken and allowed to crystallize).

In order to determine the time required for a quantitative reaction between morphine and fluoro- or chloro-dinitrobenzene we carried out first experiments with a solution of pure morphine hydrochloride, whose exact content on water-free morphine base had been established by the opial method of the *Ph. Helv. V.* To each 10.0 ml of this morphine hydrochloride solution (= 0.1272 g of morphine base) were added 26 ml of water, a solution of 0.25 g of fluoro- or chloro-dinitrobenzene in 30 ml of acetone and 4 ml of 25% ammonia. The mixture was shaken for a minute and the precipitated morphine-dinitrophenylether filtered off after various time, washed four times with 2 ml of acetone each time and dried for an hour at 80°C. When fluoro-dinitrobenzene was used the morphine-dinitrophenylether was precipitated at once, but with chloro-dinitrobenzene this took place only after some minutes. Many authors prescribe a cooling of the reaction mixture. We therefore carried out our experiments in two series, in which we allowed the morphine-dinitrophenylether to crystallize at room temperature (21°C) and in the refrigerator (+1°C) respectively. The results are assembled in table 17.

From the figures given in table 17 it can be seen that the reaction of morphine with fluoro-dinitrobenzene to form morphine-dinitrophenylether is completed after no more than half an hour, while chloro-dinitrobenzene needs at least 12 hours for complete precipitation. Cooling of the mixture holds up the reaction and is, in our opinion, required only after the precipitation is complete in order to lessen the solu-

TABLE 17

Reaction of morphine with 1-fluoro-2.4-dinitrobenzene or 1-chloro-2.4-dinitrobenzene

Temperature	Time	Morphine base found with fluoro-dinitrobenzene	Morphine base found with chloro-dinitrobenzene
		%	%
21°C	¼ h	99.8	—
	½ h	100.0	—
	1 h	100.0	*ca.* 60
	2 hrs	100.1	*ca.* 90
	4 hrs	—	92.4
	6 hrs	—	98.4
	12 hrs	—	100.0
1°C	¼ h	99.4	—
	½ h	99.8	—
	1 h	100.0	*ca.* 50
	2 hrs	—	*ca.* 80

bility of the morphine-dinitrophenylether. The mother liquors of the incomplete precipitations with chloro-dinitrobenzene were allowed to stand overnight and the morphine-dinitrophenylether which had been precipitated was determined. Thereby the morphine value obtained in the first place could in every case be brought up to 100%.

In the precipitation of morphine from opium extracts the possibility of a hindrance of precipitation had always to be reckoned with. In order to show that all the morphine-dinitrophenylether was precipitated after 45 minutes, we filtered it off after periods of 2 and 4 hours. The morphine values found were the same within the limits of error. In no case did a precipitate, insoluble in acetone, form in the mother liquor within the next two days, and paper chromatography also showed no free morphine.

During the precipitation with fluoro-dinitrobenzene the original yellow solution gradually took on a deep orange colour. After about two hours a yellow crystalline precipitate was formed on the bottom, which was clearly distinguishable from the more voluminous morphine-dinitrophenylether. In blanks without morphine the same colour change and the formation of the same crystalline yellow precipitate can be observed. The latter is insoluble in water, slightly soluble in cold alcohol and somewhat more soluble in hot alcohol, but very soluble in acetone. The precipitate, filtered off, washed with water and recrystallized from ethanol melted between 179° C and 180° C (corrected). After the admixture of pure 2.4-dinitro-aniline there was no drop in the melting-point, so that its identity was established. 2.4-dinitro-aniline is produced by the reaction of fluoro-dinitrobenzene and ammonia. With chloro-dinitrobenzene the originally pale yellow solution gradually turned purple, but we did not observe any dinitro-aniline crystallizing out even after several days.

In order to determine any effect of side alkaloids, present in varying amounts in opium, on the reaction between morphine and fluoro-dinitrobenzene, we precipitated the morphine from solutions containing a side alkaloid as well as morphine.

To each 10 ml of a morphine hydrochloride solution, whose exact content on water-free morphine base had been established by the opial method of the *Ph. Helv. V*, we added a solution of 0.1 g side alkaloid, 26 ml of water, 0.25 g of fluoro-dinitrobenzene in 30 ml of acetone and 4 ml of 25% ammonia, and filtered the precipitate after 45 minutes. In a further series of experiments we determined the morphine in a similar way in a mixture of the pure alkaloid bases with 50.0% of morphine base, corresponding to the opial of the *Ph. Helv. V*. The results obtained are assembled in table 18.

TABLE 18

Influence of side alkaloids on the reaction of morphine with 1-fluoro-2.4-dinitrobenzene

Alkaloid added	Water-free morphine base		
	Quantity taken in g	Quantity recovered in g	Quantity recovered in %
0.1 g codeine ...	0.1272	0.1270	99.9
0.1 g thebaine ...	0.1272	0.1274	100.1
0.1 g papaverine .	0.1272	0.1278	100.1
0.1 g narcotine ..	0.1272	0.1273	100.0
0.1 g narceine ...	0.1272	0.1269	99.8
Alkaloid mixture			
0.3004 g	0.1502	0.1503	100.0
0.2010 g	0.1005	0.1006	100.0
0.1007 g	0.0503	0.0501	99.9

From table 18 it can be seen that the side alkaloids present in varying amounts in opium do not influence the reaction of morphine with fluoro-dinitrobenzene; the same applies to chloro-dinitrobenzene which in any case is much less reactive. It must, however, be borne in mind that the content of side alkaloids in the opium extract is only a fraction of the added 0.1 g in the experiments just described. On the other hand the other phenolic bases present in opium may precipitate with morphine. According to Small (67), however, their content in opium is so small (0.005%), that they do not interfere.

Filtration and purification of the morphine-ether precipitate. — (The precipitate is collected quantitatively on a tared Büchner glass funnel G3 by gentle suction, washed with acetone, and dried at 80° C).

According to Mannich (50) the precipitate, formed by the reaction of morphine and chloro-dinitrobenzene, is filtered off, washed twice with 2 ml of acetone and twice with 2 ml of water and then dried. This procedure was adopted by all subsequent modifications of the Mannich method. In contrast to chloro-dinitrobenzene, fluoro-dinitrobenzene reacts with the added ammonia under formation of 2.4-dinitro-aniline, which is filtered off with the morphine-dinitrophenylether and therefore makes an intensive washing of the precipitate necessary. Garratt et al. (61) require a four-fold washing each with 2 ml of acetone. We checked this procedure by reacting morphine hydrochloride in the usual manner with fluoro-dinitrobenzene, filtering the precipitate off after 45 minutes and washing it in various ways before drying. The determination was carried out gravimetrically and by titration with perchloric acid in glacial acetic acid. The results are set out in the following table 19.

TABLE 19

Washing of morphine-dinitrophenylether formed with fluoro-dinitrobenzene

Precipitate washed with	Weight of precipitate in g (theor. 0.1673)	Morphine-dinitrophenylether	
		Gravimetric determination %	Titrimetric determination %
	0.2684	160	119.1
1 × 2 ml acetone	0.2342	140.1	109.3
2 × 2 ml acetone	0.2065	123.4	101.2
2 × 2 ml acetone / 2 × 2 ml water	0.2097	122.5	101.2
3 × 2 ml acetone	0.1791	107.1	100.3
4 × 2 ml acetone	0.1674	100.0	99.9

From all the opium samples we analysed we obtained, after washing with 4 × 2 ml of acetone, a pure, light-yellow coloured morphine-ether, whose determination, carried out in several cases by titration with perchloric acid in glacial acetic acid, always agreed well with the values found gravimetrically.

Since our experiments have shown that the modified procedure extracts all the morphine from opium and converts it quantitatively to the corresponding morphine-ether, and that a very pure substance is obtained suitable for gravimetric or titrimetric determination, we propose the following procedure.

Mannich method, modified by Büchi & Huber. — 1.000 g of opium powder (IV) is ground in a mortar with 1 ml of water to an homogeneous paste and then carefully triturated with 5 g of aluminum oxide (Woelm, acid). In the narrow part of a chromatographic tube (250 mm long, 15-20mm diameter) a pad of cotton wool is put above the tap and the tube half filled with water. 5 g of aluminum oxide (Woelm, acid) is trickled in a thin stream on the water and allowed to settle. Trapped air bubbles are removed by stirring the aluminum oxide with a glass rod. The water on top of the column is allowed to run out until the surnatant water layer is 3 cm above the surface of the aluminum oxide. The opium-aluminum oxide triturate is put in the tube and mixed with the supernatant water by stirring with a glass rod. The last remainders of the opium triturate on the pestle and in the mortar are wiped out with a pad of cotton wool moistened with water, the pad put in the tube and placed on the top of the column, using moderate pressure. The water is now allowed, if necessary under slight pressure, to run out of the chromatographic tube into a glass-stoppered, graduated measuring cylinder (capacity 100 ml) at a rate of one drop per second until the surface of the water reaches the cotton wool pad. Then the filtrate is transferred again into the chromatographic tube, allowed to run, and adding four succesive quantities each of 5 ml of water to obtain a total eluate of 35 ml. 4 ml of 25% ammonia and 0.25 g of 1-fluoro-2,4-dinitrobenzene in 30 ml of acetone are added to the eluate. Then the measuring cylinder is stoppered, shaken for one minute, and allowed to stand for at least 30 minutes at room temperature and for 15 minutes at 5°C. The morphine-dinitrophenylether formed is collected, by gentle suction and rinsing with the filtrate, on a tared Büchner glass funnel G3 and washed with four successive quantities each of 2 ml of acetone. The acetone must be drawn off within at most 15 seconds. If the precipitate has sedimentated too solidly in the glass funnel, it is whirled up with a glass rod in the washing solution.

Gravimetric determination. — The Büchner glass funnel and the precipitate are dried at 80°C for one hour and weighed after cooling in a desiccator. The percentage content of morphine in the opium powder is calculated as follows:

$$\text{Percentage of morphine} = \frac{g \times 63.2}{p}$$

where g = weight of precipitate in g
p = weight of opium taken in g

Titrimetric determination. — The washed morphine-dinitrophenylether can also be determined by titration with 0.1 N perchloric acid in a non-aqueous solvent. In this case it is of advantage to use as filter a Büchner glass funnel 1G3 or an Allihn tube 15a G3. The remaining acetone is removed by drawing air through the funnel; the precipitate is dissolved then on the filter in about 20 ml of anhydrous glacial acetic acid, the solution sucked directly into the titration vessel and the filter washed three times with 5 ml of anhydrous glacial acetic acid. 5 ml of acetic anhydride are added and the solution is titrated with 0.1 N perchloric acid potentiometrically or with crystal violet as indicator. Each ml of 0.1 N perchloric acid is equivalent to 0.02852 g $C_{17}H_{19}O_3N$ (morphine).

5.2.5. *Comparison of the morphine determination methods investigated*

In table 20 the morphine contents obtained by the method we propose are compared with those obtained by the other methods. As will be seen, higher morphine values are obtained throughout with our method than with the other methods. We believe that the method we propose extracts on the one hand all the morphine present in the opium and on the other hand determines it quantitatively. The method requires a minimum of reagents and can be easily carried out in half a day.

TABLE 20

Morphine content of the opium samples examined, in percentages as given by the various methods

(Mean values of 2-4 determinations)

Method	Opium I	Opium II	Opium III	Opium IV
Ph. Helv. V	10.18	14.36	10.70	15.58
Ph. Int. I	10.15	14.16	10.98	15.61
Brit. Ph. 1958	10.00	14.26		
U.S.P. XV	9.12	13.24		
Svenska F. XI	11.56	14.60	11.22	15.78
Eder & Wäckerlin (48)	11.66	14.24	11.24	15.89
Knaffl-Lenz (59)	10.67		10.43	
Graf (60)	11.11		9.90	15.70
Mannich (50)	11.87	14.71	11.38	16.00
Garratt and collaborators (61)	11.67	14.64	11.28	16.01
Modified method according to	12.08	14.60	11.90	16.34
Büchi & Huber	12.12	14.74	11.84	16.29
	12.06	14.68	11.94	16.40
	12.09	*14.74*	*11.89*	*16.34*

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World Health Organization Expert Committee on Addiction-producing Drugs: Tenth Report[1]

The Expert Committee on Addiction-producing Drugs of the World Health Organization held its tenth session in Geneva from 19 to 24 October 1959, and made a report which was noted by the Executive Board of the World Health Organization at its twenty-fifth session, held in Geneva from 19 January to 1 February 1960 (*resolutions EB 25 R.4 and EB 25 R.5*, Official Records of the World Health Organization, *1960*, 99).

Extracts from this report are reproduced hereafter with minor modifications. Actions modifying the scope of the international control of narcotic drugs, such as placing a new drug under control or removing it from control, will not be reported here, but in the note at the end of this volume of the Bulletin.

Work of International Bodies concerned with Narcotic Drugs

The Secretary summarized the report of the fourteenth session of the Commission on Narcotic Drugs of the Economic and Social Council;[2] the relevant resolutions of the Economic and Social Council;[2] and the latest reports of the Permanent Central Opium Board[3] and the Drug Supervisory Body.[3] Among the items of interest, note was taken of the difficulties encountered in the international control system as a result of delays by some governments in subjecting new narcotic drugs to national control. The placing of a drug under national control may be the first indication to a medical practitioner that it is addiction-producing; and when a drug comes rapidly into favour for medicinal use, as was the case with dextromoramide, any delay in the recognition of its addicting potentialities enormously accentuates the public health dangers.

In connexion with the abuse of drugs, the Committee noted that statistics on addicts in different countries were based on different criteria. It would be desirable for some common basis to be found for compiling such statistics; and it might be helpful if information on addicts who come into conflict with narcotic laws or become known in some other way could be supplemented by statistics on the number of people for whom particular drugs are prescribed on a long-term basis.

The Committee noted that some of the drugs falling under international control had never been placed on the market. In some instances it was known that producers decided not to proceed with the commercial development of a drug when a decision had been reached that it was addiction-producing. The number of such drugs may increase in the future, and the inclusion of so many drugs may result in the list of addiction-producing drugs becoming excessively long, which may be an administrative embarrassment. It would be helpful for certain purposes if the lists of controlled drugs[4,5] could be complemented by an up-to-date list of drugs actually on the market, arranged according to their international non-proprietary or common names, for the practical use of control authorities. The list should also indicate the name under which each substance is sold, and the meaning of each name in terms of base, salt or preparation. Such a list would supplement the "Multilingual list of narcotic drugs under international control"[6] until revision is possible.

The Committee noted the increasing interest in mass campaigns against opium addiction, and would point out that, for the treatment of such addicts, simple methods of withdrawal are available, which have proved to be successful under various circumstances.

Addiction Liability, Chemical Structure, and Control

In 1949, the Commission on Narcotic Drugs of the Economic and Social Council,[7] considering that varying degrees of control should be applied to different classes of substances, requested the Expert Committee on Addiction-producing Drugs "to furnish the Commission, at its fifth session, with definitions of the terms 'drug addiction', 'addiction-forming drugs', 'habit-forming drugs' and 'fundamental structure of an addiction-forming drug', and to illustrate such definitions by references to appropriate drugs".

Definitions

The Committee formulated draft definitions of drug addiction and habituation in the report on its second session,[8] and

[1] World Health Organization, *Technical Report Series* (1960), No. 188.

[2] See *Bulletin on Narcotics*, vol. XI, No. 4.

[3] See *Bulletin on Narcotics*, vol. XII, No. 1.

[4] Annex to the Permanent Central Opium Board's statistical form.

[5] List of drugs under international control, published annually by the United Nations Division of Narcotic Drugs.

[6] United Nations (1958) multilingual list of narcotic drugs under international control (document E/CN.7/341).

[7] United Nations Commission on Narcotic Drugs, Report of the Fourth Session (16 May-3 June 1949) — (Economic and Social Council, Official Records: ninth session. Supplement No. 9), Lake Success, New York (document E/1361-E/CN.7/186, p. 61).

[8] *Wld.Hlth.Org. techn.Rep.Ser.*, 1950, *21*, 6 (section 6).

attempted to clarify the distinction in its third report.[9] Revised definitions were approved in its seventh report.[10]

These definitions have had some acceptance and have served a useful purpose. However, in order to make them applicable to the various substances under international control, they had to include heterogeneous criteria, and these criteria are difficult to interpret. Even if the definitions were re-written to be specifically descriptive of the various qualitative types of addiction, all of which involve drug-induced behavioural disturbances, some difficulties would still remain regarding their applicability to control. The fundamental criterion for control is the extent to which these drug-induced behavioural disturbances are a risk to the community.

Chemical Structure

With further reference to the Commission's request, the Expert Committee, in the report on its second session,[11] said that, in the present state of our knowledge, it was not possible to say what part of the molecule of a drug was responsible for its addiction properties, but that it was known that certain drugs, having, in the main, a common structure, produced in some degree a similar addiction. At that time, examples of common structure with relation to addiction-production included the groups of which morphine, pethidine, and methadone were members. The Committee emphasized that this list was not complete, and that probably new compounds of different structure would be developed which were also addiction-producing. This has since been realized, for example, in dimenoxadol and certain benzimidazole derivatives.

In this connexion, it was said only a few years ago [12] that certain chemical characteristics are common to morphine-like analgesic and addiction-producing drugs. Since then, structures have become known which are potent in both respects, but which lack one or other of the common chemical characteristics.[13]

There is, in addition, some evidence that analgesic effect and addiction liability can be modified in one substance in opposite directions — i.e., substances have been synthesized which combine strong morphine-like analgesia with a lowered addiction liability. Substances are known which are more potent than morphine in analgesic effect, in the production of morphine-like subjective effects, in the suppression of abstinence phenomena, and in the prevention of such phenomena by substitution in morphine-addicted individuals. On these accounts alone, these substances would be rated more likely to abuse, and hence perhaps more dangerous than morphine. On the other hand, the abrupt withdrawal of these same substances (after substitution or direct addiction) results in a relatively mild abstinence syndrome, the only available measure of physical dependence. This evidence would indicate less liability to the development of physical dependence under conditions of prolonged administration.

[9] *Wld.Hlth.Org. techn.Rep.Ser.*, 1952, *57*, 9 (section 6.1).
[10] *Wld.Hlth.Org. techn.Rep.Ser.*, 1957, *116*, 9 (section 8).
[11] *Wld.Hlth.Org. techn.Rep.Ser.*, 1950, *21*, 7 (section 6.4).
[12] Eddy, N. B., Halbach, H. & Braenden, O. J. (1956), *Bull.Wld. Hlth.Org. 14*, 353.
[13] Eddy, N. B., *J.Soc.chem.Ind.* (Lond.) (in press).

Control

It should be clear from the foregoing that the primary consideration, in deciding whether a drug should be subject to control and to what degree, is liability to abuse, resulting in risk to the community.

No definition, however descriptive, can be a complete guide to what should be controlled. Similarly, in the light of our present knowledge, chemical structure *per se* cannot be the sole criterion. There are certain chemical groups of drugs — e.g., the morphine, pethidine and methadone groups — one or more members of which have been shown to be addicting. Within such groups, closely similar structures must be suspect unless and until there is convincing evidence that they are not addiction-producing. In the meantime, control measures of a provisional nature are justified.

Diverse structures are being developed which have a morphine-like action with varying degrees of addiction liability. In every case, an assessment will have to be made of the degree of risk to the community, based on liability to abuse, and consideration will have to be given to therapeutic advantages. Then, finally, it will be possible for the degree of control commensurate with the risk to the community to be established by the World Health Organization.

Research in the Field of Drug Addiction

The Committee has repeatedly stressed the need for research along various lines in the field of drug addiction. In order to contribute adequately to the World Health Organization's functions under the various international conventions controlling narcotic drugs, the Committee must have at its disposal the results of basic and applied research in this field. The Committee has had to deal repeatedly with notifications without adequate information so that decisions have had to be deferred. At present, the Committee's work depends in large measure upon the receipt of information respecting work carried out at the Addiction Research Center (United States of America), and the Department of Pharmacology of the University of Michigan (United States of America), and on the results of controlled clinical investigation, many of which are funnelled through the Committee on Drug Addiction and Narcotics of the National Research Council (United States of America). Because of their heavy workloads, these institutions, even though they have endeavoured to give priority to specific requests from the Expert Committee, have not always been in a position to furnish the Committee with the necessary information in time for it to take action as early as desirable. Thus, the preventive character of the international control measures has been hampered. In order to ameliorate this situation, means should be found to expand research activities, as outlined above, and to extend them to other parts of the world.

Moreover, the Committee emphasized again that drug addiction affects large numbers of people in many areas of the world and is, therefore, an international public health problem of great magnitude. Research in this field has not had the degree of support commensurate with its importance. The Committee therefore strongly urged that research on narcotic action and

other aspects of drug addiction should be strengthened and expanded. A few of the topics on which work could profitably be enhanced or initiated include:

Basic investigations of the mechanisms of action of addicting drugs and of drug addiction, utilizing techniques from all pertinent fields, such as pharmacology, experimental psychology, biochemistry, neurophysiology;

Epidemiology of drug addiction [14] (almost nothing has been done on this subject);

Controlled evaluations of programmes for treatment of drug addiction;

Development and calibration of methods for assessing addiction liability in animals;

Clinical evaluations of new drugs with respect to analgesic action, liability to cause side actions, and development of tolerance and physical dependence under conditions of clinical use;

Cumulation, codification and making available information on all aspects of drug addiction. An initial effort in this direction is represented by the work on "coded information on narcotics".[15]

Carriage of Narcotic Drugs in First-Aid Kits of Aircraft Engaged in International Flight

The Committee's attention was drawn to a report [16] on the principles under which opiates or similar drugs might be used and carried in first-aid kits on board aircraft engaged in international flight, and on the application of efficient safeguards against abuse. The Committee concurred with all the conclusions and suggestions, except that it was of the opinion that morphine should not be given orally, and that the dose to be used might be reconsidered with a view to its reduction to 10 mg per ampoule. The Committee was also of the opinion that a morphine antagonist (e.g., nalorphine) should be carried, and that instruction on the indications which would warrant its use should be included in the training of authorized personnel.

[14] World Health Organization, Study Group on the Treatment and Care of Drug Addicts (1957), *Wld.Hlth.Org. techn.Rep.Ser.*, *131*.

[15] Referred to as "classified information on narcotics" in the ninth report of the Expert Committee on Addiction-producing Drugs, *Wld. Hlth.Org. techn.Rep.Ser.*, 1959, *160*, 14.

[16] Unpublished working document WHO/Av.Med./1.

Proposed Single Convention on Narcotic Drugs

Schedules and Scope of Control

The Committee was pleased to note that in drafting the Single Convention on Narcotic Drugs,[17] attention had been given to the principle referred to in the present report (paragraph entitled "Control", page 4) — i.e., that the essential criterion for the establishment and degree of control is risk to the community. This consideration appears to be reflected in the implementation of schedules I to IV, where variations in the degree of the control measures applied are related to differences in the risk involved with various substances.

...

The Committee would reiterate the opinion expressed in its ninth report on the seriousness of placing a substance in schedule IV with its absolute prohibition as now drafted. When liability to abuse is great, lack of medical need and obsolescence for other purpose could justify prohibition. In any case, very careful balancing of risks against possible therapeutic advantage should be undertaken, restricting as little as possible the availability of medicaments to physicians. Where a drug appeared to represent a particularly high danger to the community, as in the case of diacetylmorphine (heroin), relevant recommendations to prohibit or restrict legitimate use could continue to be made by the international organs concerned; but decisions thereupon should not be mandatory.

In this connexion, the Committee would draw attention to the repeated references to diacetylmorphine in its reports.[19] [20] [21] The Committee reaffirmed its stand on the replaceability of this dangerous addicting agent; and the marked decrease in production of the drug, together with the small number of countries not prepared to suppress its use, indicates that the recommendation of the Commission on Narcotic Drugs of the United Nations Economic and Social Coucil [22] urging its prohibition had been very largely followed.

[17] United Nations Commission on Narcotic Drugs. The Single Convention on Narcotic Drugs (Third Draft) (mimeographed document E/CN.7/AC.3/9).

[18] *Wld.Hlth.Org. techn.Rep.Ser.*, 1959, *160*, 12 (section 10.1).

[19] *Wld.Hlth.Org. techn.Rep.Ser.*, 1956, *102*, 4 (section 3.1).

[20] *Wld.Hlth.Org. techn.Rep.Ser.*, 1957, *116*, 5 (section 4.1).

[21] *Wld.Hlth.Org. techn.Rep.Ser.*, 1958, *142*, 5 (section 4.1).

[22] United Nations Commission on Narcotic Drugs. Report on the tenth session (18 April-12 May 1955) — (Economic and Social Council Official Records: twentieth session. Supplement No. 8), Geneva, p. 42 (Document E/2768/Rev.1 — E/CN.7/303/Rev.1).

Note

Changes in the Scope of Control

The international treaties on narcotic drugs make provision for changes in the scope of control by means of a procedure which involves governments, the Secretary-General of the United Nations and the World Health Organization, in particular its Expert Committee on Addiction-producing Drugs. The procedure may be applied not only in respect of the extension of control to new drugs, but also in respect of exemption from control of drugs or their preparations.

The international procedure for extending control to new drugs is put into motion upon an application being made by a government to the Secretary-General of the United Nations, who transmits it immediately to all states parties to the relevant convention and the international bodies concerned, including the World Health Organization. The latter subsequently decides whether the substance considered is susceptible of producing addiction or of being converted into a product capable of producing addiction. If so, it is placed under one of the two existing control regimes provided in the conventions. Any positive decision is ultimately communicated by the Secretary-General of the United Nations to all governments, whereupon the drug in question enters the control system.

In the case of the exemption from control of drugs or their preparations, the procedure is similar except that as regards exemption of preparations, the World Health Organization can act on its own initiative.

During 1959, several requests were received from governments regarding extension of control to new drugs. The World Health Organization decided that:

The drugs allylprodine, benzethidine, furethidine, levophenacylmorphan, metazocine, norlevorphanol, phenazocine, piminodine and their respective salts should be placed under the more severe of the two principal regimes of control applying to narcotic drugs —viz, under that which is applicable to morphine or morphine-like drugs, in view of their dangerous addiction-forming properties. It may be noted that the drug phenazocine and its salts had previously been placed provisionally under the same control regime by the Commission on Narcotic Drugs at its fourteenth session, 27 April to 15 May 1959.

In the absence of sufficient data, no decision was made in respect of the drug 2,2-bis-diethylaminomethyl-1-phenyl-1-cyclohexylethane.

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